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THE RELATIONSHIP BETWEEN ELECTRICAL AND MECHANICAL EVENTS IN THE CARDIAC CYCLE OF MAN *

BY

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In studying the dynamics of the heart beat, the relationship between electrical and mechanical events in the cardiac cycle has been of fundamental importance. The basic concepts of this relationship have been defined by Lewis (1925) and Wiggers (1923) and their co-workers. Sir Thomas Lewis provided indirect information on these events in the right auricle of man. Animal experiments, supplemented by such indirect information as could be obtained from venous and arterial pulse wave tracings, recording of heart sounds, etc., in man were used by Wiggers to anticipate the probable normal sequence of events in the cardiac cycle.

More precise information may now be obtained using the method of right heart catheterization. With direct measurements from within the right heart chambers and pulmonary artery, coupled with peripheral arterial pulse wave and electrocardiographic recordings, the normal course of electrical and mechanical events may be more clearly defined in man and abnormalities in contraction and conduction of the diseased heart may be further elucidated.

The data thus obtained will supplement the results obtained by many other investigators and will be analysed and discussed in the light of their studies.

METHOD OF STUDY

In this study recordings of blood pressures in the auricle, ventricle, pulmonary artery, and brachial artery were made simultaneously with the electrocardiogram. The method of catheterization of the right heart, introduction of the indwelling arterial needle, and recording of pressures has been previously described (Cournand and Ranges, 1941; Cournand *et al.*, 1944; and Bloomfield *et al.*, 1946). In some instances a double lumen catheter was used (Cournand *et al.*, 1945), permitting the simultaneous recording of pressures in the right auricle and ventricle or the right ventricle and pulmonary artery. In order to obtain satisfactory records of these pressures, manometers of varying sensitivities were used. Only the records that permitted the exact determination of the onset of rise of pressure in the right heart or in the arteries were used. The electrocardiograph was of the string galvanometer type and tracings were usually made on standard lead II. The speed of the camera could be varied from 12·5 to 50 mm. a second, permitting time intervals to be estimated correctly to within 0·010 sec. It has been shown repeatedly that no parallax exists between the light beams of the manometers and the electrocardiograph. A method for determining the time lag in mechanical transmission of an impulse through the catheter at 37° C. has been previously described (Cournand *et al.*, 1946), and on repeated determinations was found to be 0·010 sec. This applies to the initial pressure rise only. In analysing the records, a correction was therefore made by subtracting 0·010 sec. from the measured values of the time intervals between the beginning of electrical and the beginning of mechanical events. In the present state of recording blood pressures in the right heart it is possible to determine exactly the point at which an initial pressure rise takes place. Because there is great uncertainty as to the accuracy of the records during the period of decline of pressure, analysis of the pressure curves during diastole was not attempted.

* This work was supported by a grant from the Commonwealth Fund with additional aid from the Life Insurance Medical Research Fund.

† French Government Research Fellow in Medicine.

The following measurements were made in analysing the records and the following symbols will be used in presenting the data.

Beginning of the P wave of the electrocardiogram	P
Beginning of the Q wave of the electrocardiogram, or R, if Q is absent	Q
Beginning of auricular systole, marked by an ascension of the intra-auricular pressure wave near the end of the diastolic period	At_S
Beginning of right ventricular systole, occurring at the end of diastole when the curve shows a steep rise	RV_S
Beginning of ejection in the pulmonary artery, marked by the rise of pressure in the artery, at the end of the descending diastolic curve	PA_S
Beginning of the systolic pressure rise in the brachial artery at the end of the descending diastolic curve	BA_S
Beginning of the systolic pressure rise in the femoral artery at the end of the descending diastolic curve	FA_S

The material for study was selected by analysis of all the records that had been obtained in the course of several years from normal subjects, children with congenital heart disease, and a variety of patients with cardiac or pulmonary disease.

1. Relationship Between Electrical and Mechanical Events in Adults with Essentially Normal Circulation

In Table I will be found the average figures relating electrical and mechanical events in subjects with essentially normal circulation. Representative normal tracings are illustrated in Fig. 1 and 3.

(*a*) The average time interval between *the beginning of the P wave and the beginning of the auricular systole* (*P–At*$_s$) was 0·090 sec. in 16 cases. This interval is somewhat less than that of 0·110 sec., found previously in 8 adult subjects with normal hearts by Cournand *et al.* (1946). Lewis (1925) has previously described the following relationship in dogs: "The upstroke of P precedes the curve of shortening in the right auricular appendage, in six dogs, by from 0·024 to 0·043 sec." The above values are about one third of what was found in normal adults in this study. Lewis also states that in man, "the upstroke of P precedes the upstroke of 'a' in the human jugular curve by from 0·100 to 0·150 sec."

In order to evaluate the pulse wave velocity in the large veins, tracings were taken in some of the present studies as the catheter was progressively withdrawn from the right auricle to the axillary region. Although such tracings are few, figures indicate that the pulse wave velocity in the undistended large veins of normal man progresses at approximately 2·5 metres a second. Assuming an average distance of 10 cm. from the right auricle to the bulb of the right jugular vein, approximately 0·040 sec. should be added to figures obtained by the catheterization technique in order to compare them with Lewis' figures in man.

(*b*) The average time interval between *the beginning of Q and the beginning of the right ventricular systole* (*Q–RV*$_s$) was 0·075 sec. in 30 cases. Lewis (1925) states that, "the beginning of the initial ventricular deflection usually precedes the onset of ventricular contraction, as estimated from myocardiograms from the front of the ventricle in six dogs, by from 0·020 to 0·038 of a second." Kahn *et al.* (quoted by Wiggers, 1923), recording pressures by means of a needle in the right ventricle of dogs simultaneously with an electrocardiogram, found that the time interval from Q to the rise of pressure

TABLE I

Relationship Between Electrical and Mechanical Events in Adults with Essentially Normal Circulation

Heart rate per minute	Average of 30 cases	80	—
P–R interval, sec.	Average of 30 cases	0·160	—
QRS interval, sec.	Average of 30 cases	0·080	—
Q–BA_S interval, sec.	Average of 30 cases	0·160	0·140–0·190
P–At_S interval, sec.	Average of 16 cases	0·090	0·050–0·120
Q–RV_S interval, sec.	Average of 30 cases	0·075	0·060–0·100
	Average of 15 cases*	0·072	—
Q–PA_S interval, sec.	Average of 15 cases*	0·085	0·070–0·100
End diastolic pressure in			
Right ventricle, mm. Hg.	Average of 15 cases*	3·0	—
Pulmonary artery, mm. Hg.		8·0	—
Duration of isometric contraction of right ventricle, sec.	Average of 15 cases*	0·013	0·010–0·020

* The same 15 cases were used to obtain these values.

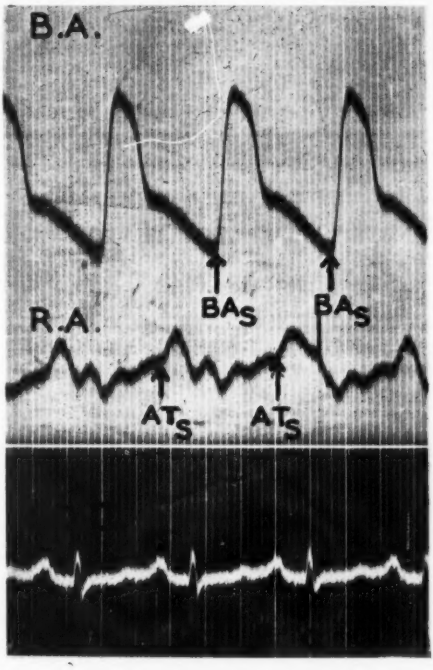

FIG. 1.—Record illustrating normal electrical-mechanical time intervals in an adult subject.
From top to bottom, blood pressure tracings in the brachial artery (B.A.) and the right atrium (R.A.), and electrocardiogram lead II.
$P\text{–}At_S = 0{\cdot}080$ sec. $Q\text{–}BA_S = 0{\cdot}160$ sec.
In this and all other records the distance between vertical lines is equal to 0·040 sec.

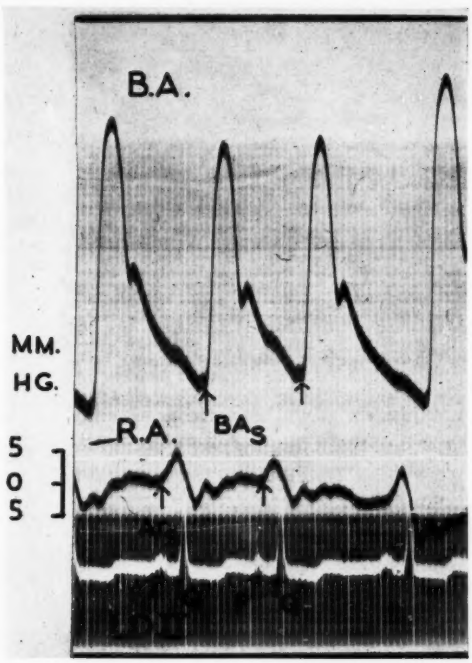

FIG. 2.—Record illustrating electrical-mechanical events in a case with auricular premature contractions.
From top to bottom, blood pressure tracings in the brachial artery (B.A.), the right atrium (R.A.), and electrocardiogram lead II. P′ and Q′ correspond to the premature beat.

was from 0·031 to 0·035 sec. Garten (quoted by Wiggers, 1923), using an electrical manometer, found approximately the same interval—0·030 to 0·045 sec. An analysis of a tracing of Wiggers (1928) shows the same interval to be 0·040 sec. These figures in dogs are about one half of the values found in man in the present study. In an analysis of the time interval between the beginning of the electrical ventricular complex and the c wave in jugular tracings of man, Lewis states that, " the upstroke of R precedes the upstroke of c in the human jugular by from 0·100 to 0·150 of a second." Miller and White (1941) found an identical value for the Q–c interval in man. Assuming that the c wave corresponds to the beginning of the mechanical contraction in the right ventricle and subtracting 0·040 sec. for its transmission to the jugular, the figures compare well with the $Q\text{–}RV_s$ time as measured directly.

(*c*) The average time interval between *the beginning of Q and the beginning of the pulmonary artery systole* ($Q\text{–}PA_s$) was 0·085 sec. Using this time interval, it is possible to measure the duration of the isometric contraction of the right ventricle, i.e. the time required to raise the pressure from the end diastolic level in the right ventricle to the end diastolic level in the pulmonary artery. This time is calculated by subtracting the value of $Q\text{–}RV_s$ from $Q\text{–}PA_s$. In 15 cases where both right ventricle and pulmonary artery pressures have been measured, the value for this interval was 0·013 sec. A tracing of simultaneous pulmonary artery and right ventricular pressures, taken with a double lumen catheter (Fig. 3), demonstrates the short duration (0·010 sec.) of the isometric contraction in a normal subject. In the 15 cases studied, the average pressure values were, respectively, 3 mm. Hg for the end diastolic pressure in the ventricle and 8 mm. Hg for the end diastolic pressure in the pulmonary artery. A period

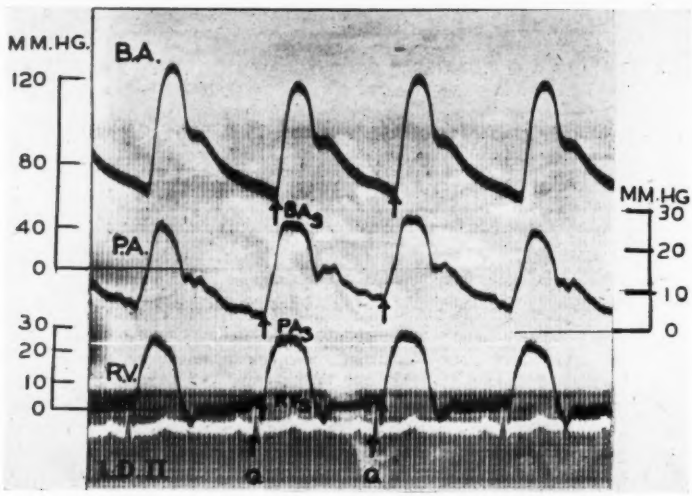

FIG. 3.—Record illustrating normal electrical-mechanical time intervals in an adult subject.

From top to bottom, blood pressure tracings in the brachial artery (B.A.), the pulmonary artery (P.A.), the right ventricle (R.V.), and the electrocardiogram lead II. The intracardiac blood pressure tracings were taken simultaneously with a double lumen catheter.

Note that the slope of the ascending pressure curves in the right ventricle and pulmonary artery do not exactly coincide. This may represent a genuine difference or be a manifestation of hysteresis in the recording. Regardless of the interpretation given to this difference, it has no bearing upon the choice of the exact site of the initial rise in pressure.

$Q–RV_S = 0{\cdot}080$ sec. $Q–PA_S = 0{\cdot}090$ sec. $Q–BA_S = 0{\cdot}160$ sec.

The duration of isometric contraction is 0·010 sec.

of 0·013 sec. was therefore necessary to raise the pressure in the right ventricle 5 mm. Hg above the initial level in order to open the pulmonary valves.

(*d*) The average time interval between *the beginning of Q and the beginning of brachial artery systole* ($Q–BA_s$) was found to be 0·160 sec. in 30 cases. Assuming that the pulse wave velocity does not vary greatly, this time interval is probably valuable in assessing indirectly the duration of isometric contraction of the left ventricle. By simultaneous registration of heart sounds, subclavian pulse, and the electrocardiogram in man, Wiggers (1944) estimated the duration of isometric contraction in the left ventricle to be from 0·040 to 0·060 sec. Katz and Feil (1923) found figures with a somewhat greater range, 0·024 to 0·089 sec. With an average duration of isometric contraction of the left ventricle of 0·050 sec., 0·110 sec. would be required for the pulse wave to be transmitted to the brachial artery. This corresponds approximately to a pulse wave velocity of 5 metres a second. Previously published values for the time interval between the beginning of Q and the onset of pressure rise in the more proximal arteries will be found in Table II.

2. RELATIONSHIP BETWEEN ELECTRICAL AND MECHANICAL EVENTS IN CHILDREN WITH CONGENITAL HEART DISEASE

In Table III will be found the average figures in children whose ages range from 5 months to 16 years. On the whole, the intervals were shorter than in normal adults.

(*a*) *The average* $P–AT_s$ *time interval* was 0·060 sec. in 16 cases. In a previously reported case of a child 8 years of age with tetralogy of Fallot, a value of 0·055 sec. was found, Cournand *et al.*, 1946. The question arose as to whether the $P–AT_S$ time varies with the age of the subjects. In general it was found that the younger the child the shorter the $P–AT_S$ time although the correlation did not appear to be extremely close. In Fig. 4 is illustrated the $P–AT_S$ time interval in a child of 3. In general, the nature of the congenital disease did not appear to exert a great influence on this time interval. In two

TABLE II

PREVIOUSLY PUBLISHED VALUES FOR THE TIME INTERVAL BETWEEN THE BEGINNING OF Q AND THE ONSET OF ARTERIAL PRESSURE RISE (IN SECONDS)

Author	Interval studied	Range	Average
Nichol (1933)	Q to rise of pressure in subclavian artery	0·119–0·166	0·135
Wolferth *et al.* (1935)	Q to rise of pressure in carotid artery	0·090–0·150	0·111
Katz *et al.* (1935)	Q to rise of pressure in subclavian artery	0·100–0·160	0·120
Battro *et al.* (1936)	Q to rise of pressure in carotid artery	0·060–0·120	—
Castex *et al.* (1941)	Q to rise of pressure in carotid artery	0·080–0·160	0·120
Kossmann *et al.* (1947)	Q to rise of pressure in carotid artery	0·131–0·148	0·139
Present study (1948)..	Q to rise of pressure in brachial artery	0·140–0·190	0·160

TABLE III

RELATIONSHIP BETWEEN ELECTRICAL AND MECHANICAL EVENTS IN CHILDREN WITH CONGENITAL HEART DISEASE

Heart rate per minute	Average of 23 cases	109	—
PR interval, sec.	Average of 23 cases	0·140	—
QRS interval, sec.	Average of 23 cases	0·060	—
Q–BA_S interval, sec.	Average of 23 cases	0·150	0·140–0·190
P–At_S interval, sec.	Average of 16 cases	0·060	0·030–0·090
Q–RV_S interval, sec.	Average of 23 cases	0·058	0·040–0·100
	Average of 12 cases*	0·056	—
Q–PA_S interval, sec.	Average of 12 cases*	0·079	0·050–0·110
End diastolic pressure in			
Right ventricle, mm. Hg.	Average of 12 cases*	5·0	—
Pulmonary artery, mm. Hg.		18·0	—
Duration of isometric contraction of right ventricle, sec.	Average of 12 cases*	0·023	0·010–0·030

* The same 12 cases were used to obtain these values.

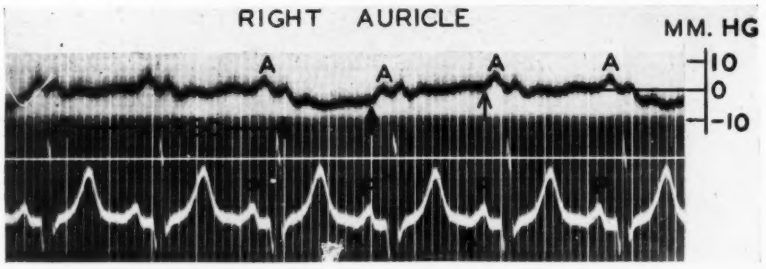

FIG. 4.—Record illustrating electrical-mechanical time intervals in a child of 3 years with congenital heart disease.

From top to bottom, blood pressure tracings in the right atrium and electrocardiogram lead II. The electrocardiographic standardization is 1 millivolt = 2 centimetres.

cases of interauricular septal defect the P–AT_S times in the right and in the left auricles were identical, i.e. 0·060 sec.

(*b*) *The average Q–RV_S time interval*, extending from the initial deflection of the QRS complex to the beginning of right ventricular systole was 0·058 sec. in 23 cases. No significant relationship could be found between this time interval and the nature of the defect or the age of the subject. It is, however, important to note that in all types of congenital defects, even in the cases with hypertrophy and dilatation of the right ventricle, the duration of Q–RV_S was never greater than in normal adults. In one case of interventricular septal defect the

$Q–V_s$ time intervals were the same in the right and in the left ventricle, i.e. 0·070 sec. (Fig. 5).

For lack of knowledge of the exact onset of the initial electrical deflection corresponding to activation in each of the four separate chambers of the heart, no conclusion can be drawn from the figures given in this and the previous section as to the spread of excitation and beginning of contraction in each chamber.

(*c*) *The average $Q–PA_s$ time interval* was 0·079 sec. in 12 cases. The difference between this figure and the $Q–RV_s$ time interval in these 12 cases, represented an average duration of isometric contraction in the right ventricle of 0·023 sec., with a range of 0·010 to 0·030 sec. Since the average pressure values at the end of diastole in the right ventricle and in the pulmonary artery were 5 mm. Hg. and 18 mm. Hg. respectively, this time interval (0·023 sec.) was required to raise the pressure in the right ventricle by 13 mm. Hg. This increase in the duration of isometric contraction was therefore due to hypertension in the lesser circulation. In a case of patent ductus arteriosus studied before and after ligation a change in the duration of isometric contraction was noted. As seen in Table IV, 0·030 sec. was required to raise the pressure in the right ventricle 36 mm. Hg. before operation. After ligation the duration of isometric contraction was reduced to 0·010 sec. for a pressure rise in the right ventricle from 1 to 5 mm. Hg.

(*d*) *The average $Q–BA_s$ time* was 0·150 sec. in 23 cases. This figure is almost identical with that found in adults, although the distance between the heart and the peripheral artery is obviously less. If one assumes that the time of isometric contraction in the left ventricle is approximately the same in children as in adults, then the pulse wave velocity must be much slower in children. This finding is not unexpected because of the greater deformability of the arterial walls in young subjects.

3. Relationship Between Electrical and Mechanical Events in Adult Patients with Cardiovascular Disease

(*a*) *Normal Sinus Rhythm with no Conduction Abnormalities*

In Table V will be found the average figures relating electrical and mechanical events in a group

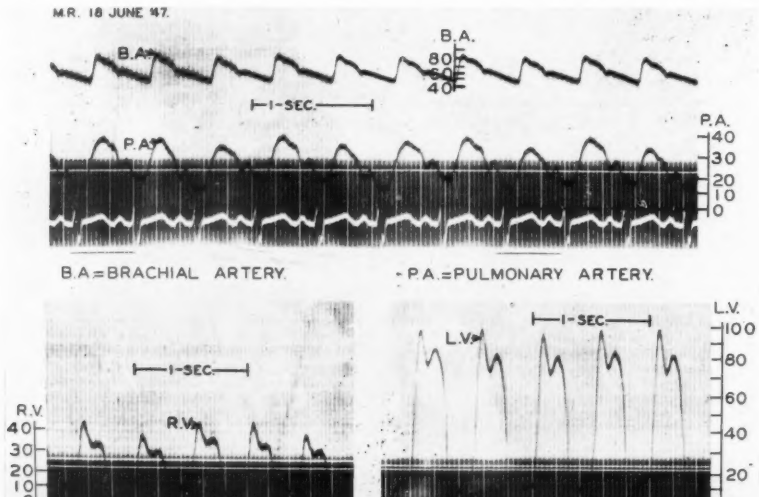

FIG. 5.—Records illustrating electrical-mechanical events in a case with interventricular septal defect.

Upper row from top to bottom, blood pressure tracings in the brachial artery (B.A.) and the pulmonary artery (P.A.). Lower row: at left, blood pressure tracing in the right ventricle (R.V.), at right, blood pressure tracing in the left ventricle (L.V.). Note that the tracings in the ventricles may show some evidence of overshooting.

$Q–RV_s = 0·070$ sec. $Q–PA_s = 0·080$ sec. $Q–LV_s = 0·070$ sec. $Q–BA_s = 0·150$ sec.

R.V. = Right ventricle. L.V. = Left ventricle.

All pressures in mm. Hg. Electrocardiogram, lead II.

TABLE IV

RELATIONSHIP BETWEEN ELECTRICAL AND MECHANICAL EVENTS BEFORE AND AFTER LIGATION IN A CASE OF PATENT DUCTUS ARTERIOSUS

	Before ligation	After ligation
Q–RV_S interval, sec.	0·060	0·050
Q–PA_S interval, sec.	0·090	0·060
Duration of isometric contraction of right ventricle, sec.	0·030	0·010
End diastolic pressure in		
Right ventricle, mm. Hg.	0	1·0
Pulmonary artery, mm. Hg.	36·0	5·0

TABLE V

RELATIONSHIP BETWEEN ELECTRICAL AND MECHANICAL EVENTS IN ADULTS WITH CARDIOVASCULAR DISEASE

Heart rate per minute	Average of 21 cases	85	—
PR interval, sec.	Average of 21 cases	0·180	—
QRS interval, sec.	Average of 21 cases	0·080	—
Q–BA_S interval, sec.	Average of 21 cases	0·170	0·140–0·210
P–At_S interval, sec.	Average of 21 cases	0·083	0·050–0·100
With normal right heart pressures			
Q–RV_S interval, sec.	Average of 8 cases	0·074	0·070–0·090
Q–PA_S interval, sec.	Average of 8 cases	0·088	0·080–0·110
End diastolic pressure in			
Right ventricle, mm. Hg.	Average of 8 cases	3·0	—
Pulmonary artery, mm. Hg.	Average of 8 cases	7·0	—
Duration of isometric contraction of right ventricle, sec.	Average of 8 cases	0·014	0·010–0·020
With elevated right heart pressures			
Q–RV_S interval, sec.	Average of 13 cases	0·073	0·060–0·090
Q–PA_S interval, sec.	Average of 13 cases	0·096	0·080–0·120
End diastolic pressure in			
Right ventricle, mm. Hg.	Average of 13 cases	7·0	—
Pulmonary artery, mm. Hg.	Average of 13 cases	32·0	—
Duration of isometric contraction of right ventricle, sec.	Average of 13 cases	0·023	0·010–0·050

of 21 patients with various types of cardiovascular disease including congenital, rheumatic, hypertensive, arteriosclerotic, and cor pulmonale.

In all these patients the P–At_S, Q–RV_S, and Q–BA_S time intervals were approximately the same as in normal adults regardless of the presence or absence of cardiac failure.

The Q–PA_S time interval studied in 8 cases of heart disease with normal right heart and pulmonary artery pressures (without evidence of congestive failure) was identical with the figure found in normal adults. In 13 patients with elevated right heart and pulmonary artery pressures and evidence of congestive failure, the average Q–PA_S time interval was slightly prolonged although the range did not differ greatly from the normals.

The average duration of the isometric contraction of the right ventricle in cardiacs with normal right heart pressures was 0·014 sec., essentially a normal figure. This interval was required to raise the pressure in the right ventricle from an average of 3 to 7 mm. Hg. In the patients with congestive failure an average of 0·023 sec. was required to raise the pressure from 7 to 32 mm. Hg. a difference of 25 mm. This figure falls within the normal variation but the range was greater, and in some cases with hypertension of the lesser circulation, isometric contraction was markedly prolonged. As can be seen in Fig. 10 (see p. 12), there appears to be a trend of correlation between the duration of isometric contraction of the right ventricle and the magnitude of the pressure difference between the end diastolic levels of the right ventricle and the pulmonary artery.

(b) Abnormalities of Rhythm, Conduction, and Contraction. (1) *Auricular premature contractions*

Auricular premature beats were observed in three patients. In two, pressures were recorded in the right auricle, and in the third in the right auricle and right ventricle. A representative tracing is seen in

Fig. 2 (see p. 3). There was no demonstrable difference in the P–At_s, Q–RV_s, and Q–BA_s time intervals in the premature beat as compared to the sinus beat. It should be noted that in all these cases the degree of prematurity was not marked.

(2) *Ventricular premature contractions*

The data that form the basis of this analysis were accumulated at random. It is therefore obvious that a systematic study, using more complete electrocardiographic data (conventional and endocardial leads), is required to confirm and amplify the findings reported here. In particular the problem of induced right ventricular premature contractions should be greatly clarified by a well planned study.

In this report emphasis will be placed only upon the following points: (*a*) asynchronism of the two ventricles, (*b*) nature and character of auricular events during the premature ventricular contractions, (*c*) relationship between premature contraction and arterial systolic rise.

(*a*) *Ventricular asynchronism and its relationship to the site of origin of the premature ventricular contractions.* The type of ventricular asynchronism produced by premature ventricular contractions can be identified by examination of mechanical events recorded simultaneously on both sides of the heart. A prolongation of the Q–RV_s time alone suggests a delay in contraction of the right ventricle, while prolongation of the Q–BA_s time points to a delay in left ventricular contraction.

However, in order to compare the Q–BA_s time interval of the normal beat and the premature contraction, it was necessary to read the Q–BA_s times at the same pressure levels. Since the diastolic

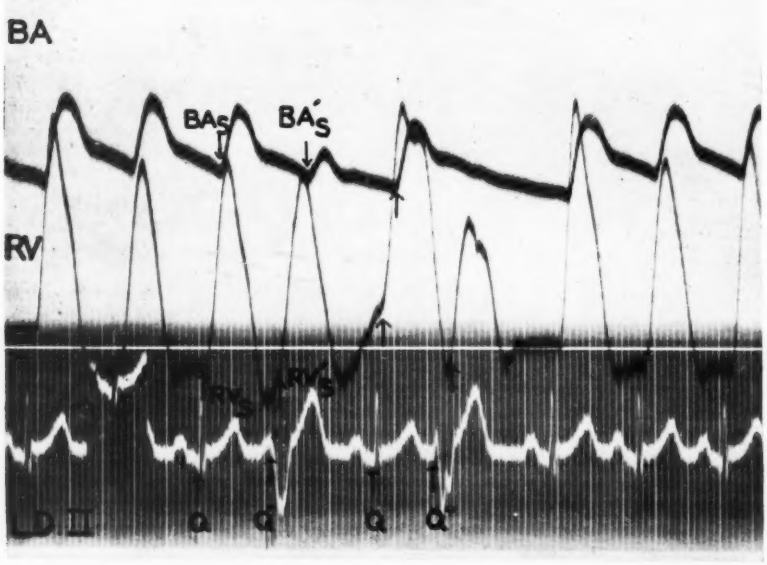

FIG. 6.—Record illustrating electrical-mechanical events in a case with ventricular premature contractions.

From top to bottom, blood pressure tracings in the brachial artery (B.A.), the right ventricle (R.V.), and electrocardiogram lead II. Q′ and Q″ correspond to premature contractions.

Q–BA_s = 0·130 sec. Q–RV_s = 0·060 sec. Q′–BA_s = 0·210 sec. Q′–RV_s = 0·060 sec.
Q–Q′ = 0·44 sec. Q–Q″ = 0·38 sec.

Note that Q″ is not followed by demonstrable pulse wave in the brachial artery and corresponds to a low pressure rise in the right ventricle.

pressure in the aorta will be higher the earlier the premature contraction, it was arbitrarily decided to read the $Q–BA_S$ time for the normal beat at the initial pressure level of the premature beat.

The majority of ventricular premature beats studied, showed as the striking characteristic, a lengthening of the $Q–BA_S$ time (average of 9 cases, 0·227 sec., range 0·180 to 0·270 sec.) while the $Q–RV_S$ time remained normal (average of 9 cases, 0·074 sec., range 0·060 to 0·100 sec.). An illustrative example is shown in Fig. 6.

However, in one patient in whom numerous premature beats were observed, the $Q–BA_S$ time intervals in the sinus and premature beats were respectively 0·140 and 0·150 sec. In contrast, the $Q–RV_S$ time of the sinus beats varied from 0·060 to 0·070 sec. while the $Q–RV_S$ times of the premature beats were 0·070 to 0·100 sec.

In summary, the ventricular asynchronism found suggests that there was a delay in left ventricular contraction in the first group of 9 patients, whereas in one case the observations point to a delay in right ventricular contraction. Whether the delay was due to abnormalities of contraction or spread of excitation or both, is a matter of conjecture.

The relationship between the type of ventricular asynchronism and the site of origin of the ventricular premature beats is of considerable interest. In the first group of 9 patients the site of origin of most of these spontaneous premature contractions could not be identified since the majority of pressure recordings were made simultaneously with lead II of the electrocardiograph. However, the type of ventricular asynchronism suggests a right ventricular origin for these beats.

In the single patient previously discussed, the type of ventricular asynchronism suggests a left ventricular origin for all the premature beats. However, the successive premature contractions as recorded on lead I were of such different electrical configurations as to suggest both right and left ventricular origins. In addition, in a second case a similar situation was found. In this instance two isolated premature beats with QRS deflections in opposite directions were recorded in lead I (Fig. 7). It is seen that while the normal beat shows a $Q–RV_S$ time interval of 0·070 sec. the same interval measures 0·170 sec. in the first premature beat and 0·150 sec. in the second. There was no pressure wave in the brachial artery tracing corresponding to the ectopic beats, indicating absence of ejection into the aorta and, therefore, no information as to the events in the left ventricle could be obtained.

It is obvious from the two cases just cited that it is difficult to interpret the relationship between electrical configuration of the premature contractions and the mechanical events, since different electrical patterns gave the same type of ventricular asynchronism.

In the only investigations so far reported in man relating to this type of asynchronism, Castex, Battro, and Gonzales (1941) have shown that in premature

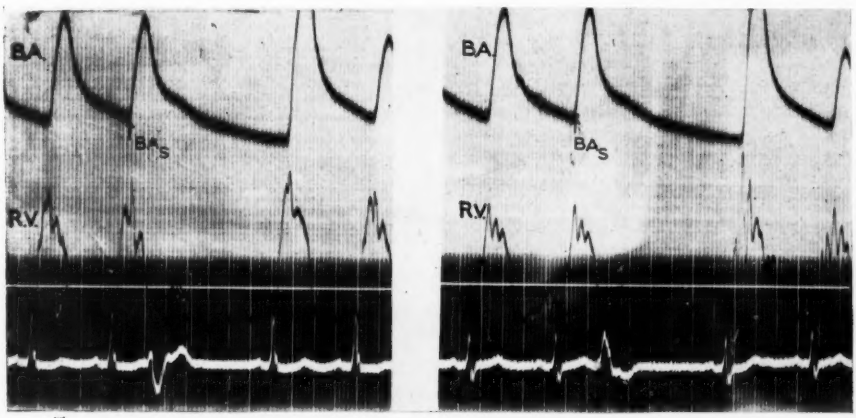

FIG. 7.—Records illustrating electrical-mechanical events in a case with ventricular premature contractions characterized by different electrical patterns.

From top to bottom, blood pressure tracings in the brachial artery (B.A.), the right ventricle (R.V.), and electrocardiogram lead I.

In the electrocardiogram to the right an S wave has appeared, indicating right bundle branch block induced by quinidine. Ventricular tracings show many artifacts, but the early systolic pressure rise can be defined.

beats there is a very significant increase in the time interval between the onset of the QRS complex and the beginning of pressure rise in the subclavian artery. In 76 normal subjects the time interval averaged 0·120 sec., while in 10 cases of right ventricular premature contractions, it averaged 0·220 sec. An unexpected finding was the prolongation of the time interval between Q and the pressure rise in the subclavian artery in 13 cases of left ventricular premature contractions.

(*b*) *Nature and character of auricular events during the premature ventricular contractions.* In 6 cases of ventricular premature beats, tracings of right auricular pressure waves showed a rise in pressure, A′, occurring during and immediately following ectopic ventricular complexes. This is in contrast to the usual drop in pressure accompanying the descent of the base at the onset of ventricular systole. Examples of such tracings are seen in Fig. 8 and 9. The question arises as to whether these pressure waves, A′, were related to tricuspid insufficiency, bulging of the valve during ventricular isometric contraction, or to auricular systole of sinus or retrograde origin. In some instances a P wave could be detected in the S–T segment of the premature beats. These P waves preceded by the usual P–AT_S time interval, the auricular pressure rise, A′. In other instances no auricular deflection could be identified within the QRS complex or S–T segment. In both instances the time interval separating the previous auricular systole and A′ was identical with the distance between the normal auricular systoles regardless of the time at which the ventricular premature contraction appeared. This indicates that A′ in these instances is the result of a normal auricular systole.

These findings are in agreement with observations of Lewis (1925) on premature beats as illustrated in his monograph (Fig. 182, page 212). In summary, it can be assumed that even when a premature ventricular beat occurs, the spread of stimulation from the sinus node may take place undisturbed and initiate a normal auricular contraction.

(*c*) *Relationship between ventricular ejection and degree of prematurity.* It is a clinically established fact that some premature beats are followed by ejection of blood into the aorta, while some are not. With simultaneous recordings of the electrocardiogram and pulse waves in brachial artery and pulmonary artery, it is possible to obtain information concerning the shortest time interval between a normal sinus and a premature beat (Q–Q′ interval) that gives rise to ejection of blood from the right and left ventricles, and the relation between this time interval and the heart rate. Table VI and Fig. 11 give data obtained in 9 patients concerning these problems. All the tracings showed several premature contractions occurring at various intervals after the sinus beats. In three of these cases pulmonary artery tracings were also available. It is seen that the shortest time interval between a sinus beat and a premature beat followed by left or right ventricular ejection varied with the rate and ranged between

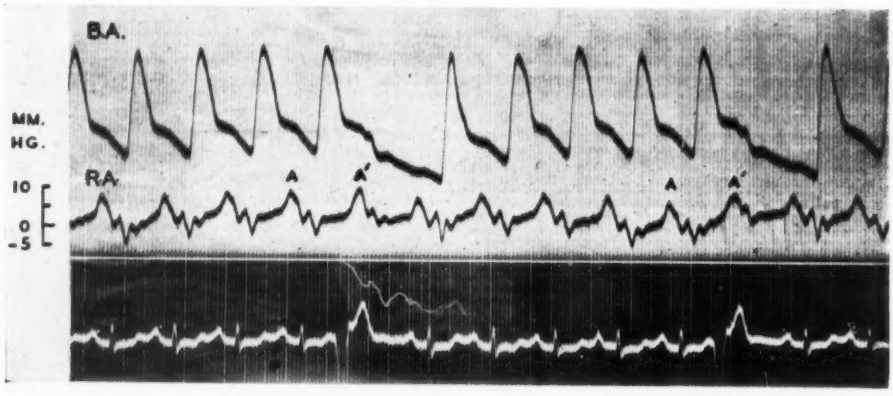

FIG. 8.—Record illustrating electrical-mechanical events in the atrium in a case with ventricular premature contractions.

From top to bottom, blood pressure tracings in the brachial artery (B.A.), right atrium (R.A.), and electrocardiogram lead II.

Note that the interval A–A′ is equal to the normal auricular cycle time indicating that the sinus rhythm is undisturbed by premature contractions.

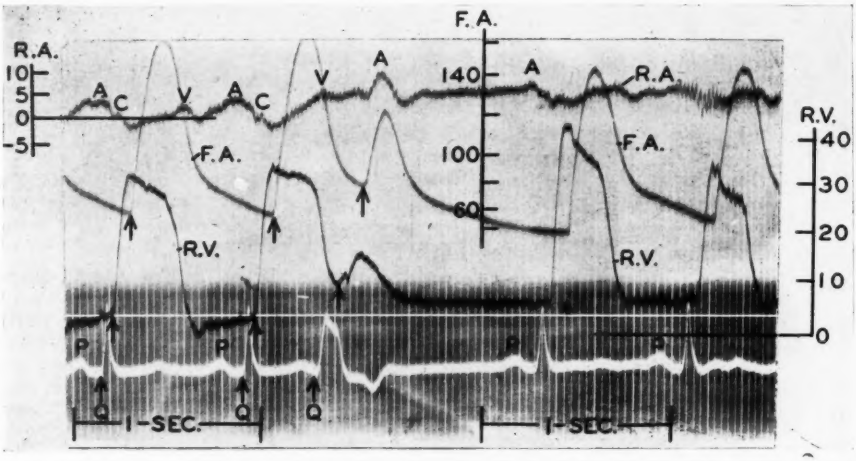

FIG. 9.—Record illustrating electrical-mechanical events in a case with ventricular premature contractions.

From top to bottom, blood pressure tracings from the right atrium (R.A.), the femoral artery (F.A.), the right ventricle (R.V.), and electrocardiogram lead II. For discussion see text. The blood pressure tracings in the right atrium and right ventricle were taken with a double lumen catheter.

Note that the brachial artery tracing shows left ventricular output following the premature contraction and that the corresponding right ventricular pressure curve starts during isometric relaxation. This is strong evidence in favour of the presence of residual blood at the time of the premature contraction.

F.A. = Femoral artery. R.V. = Right ventricle. R.A. = Right auricle. Electrocardiogram, lead II. A–C–V waves marked on R. Aur. All pressures in mm. Hg.

TABLE VI

RELATIONSHIP BETWEEN HEART RATE AND THE MINIMUM EJECTION TIME IN THE BRACHIAL AND PULMONARY ARTERIES IN NINE CASES WITH VENTRICULAR PREMATURE BEATS

Case no.	Duration of the normal cycle, sec.	Heart rate per minute	Shortest Q–Q′* interval followed by ejection in the:	
			Brachial artery, sec.	Pulmonary artery, sec.
317	0·460	130	0·340	0·340
315	0·540	111	0·400	—
348	0·680	88	0·440	0·440
345	0·720	83	0·410	—
316	0·760	79	0·510	0·480
350	0·780	78	0·480	—
306	0·780	78	0·450	—
313	0·920	65	0·500	—
320	1·040	58	0·640	—

* Q–Q′ interval is the time interval between the beginning of the QRS of the sinus beat and the beginning of the QRS of the ventricular premature beat.

0·340 sec. at 130 beats a minute and 0·640 sec. at 58 beats a minute. The remarkable straight line relationship of all intermediate points is well illustrated in the graph (Fig. 11).

In summary, at a rapid rate an early premature beat was followed by ejection of blood into the aorta and pulmonary artery; whereas, at a slower rate, a ventricular contraction with the same degree of prematurity did not produce a pressure rise in the arterial tracings. These observations can best be explained by the more rapid early diastolic filling of the heart at faster rates.

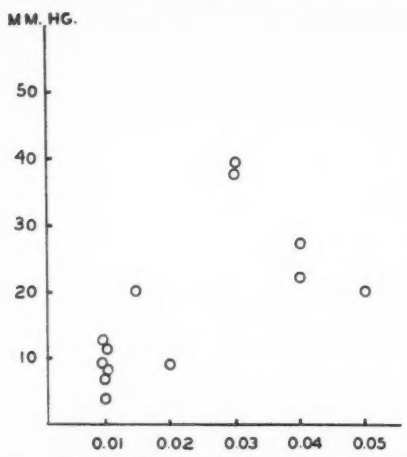

FIG. 10.—Correlation between the duration of isometric contraction and the corresponding pressure rise in the right ventricle in thirteen subjects including normal cases and cases with cardiac failure. The vertical scale shows the end diastolic pressure difference between the right ventricle and the pulmonary artery. The horizontal scale shows the isometric contraction time in seconds. For discussion see text.

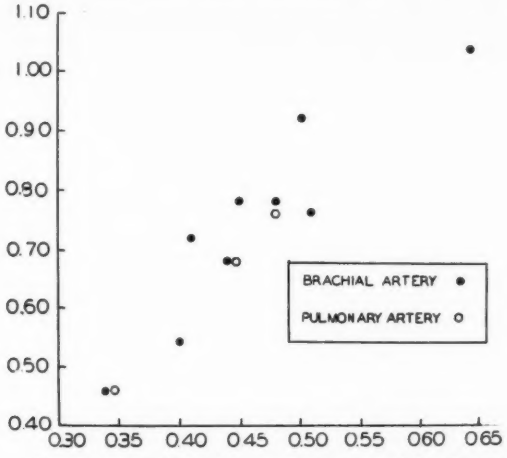

FIG. 11.—Correlation between heart rate and the shortest time interval between a normal beat and a premature contraction resulting in ejection of blood into the aorta or pulmonary artery. The horizontal scale shows the Q–Q′ interval in seconds: the vertical scale shows the duration of the normal cycle in seconds.

(3) *Auricular Fibrillation*

A study of the relationship between cycle length and Q–RV_S and Q–BA_S time intervals was made in three cases of arteriosclerotic heart disease with chronic auricular fibrillation. Significant variations as large as 0·070 sec. were found in the Q–RV_S and Q–BA_S intervals of successive beats, although the QRS complexes had essentially the same configuration and duration. No constant relationship was found between cycle length and these variations in the electrical-mechanical time intervals. In addition, the Q–RV_S and Q–BA_S intervals of the same beat did not vary to the same degree, as illustrated in Fig. 12. These findings suggest that, besides the complete arrhythmia, disturbances of the contraction mechanism of both ventricles were present.

(4) *Auricular Flutter*

Two cases of auricular flutter were studied. In one of the cases observations were made on the P–AT_S time during a period with pure flutter and a 4: 1 A-V response. The electrocardiogram and right auricular tracings are shown in Fig. 13 and demonstrate the regular sequence of electrical and mechanical events. The duration of the P–AT_S time of each auricular systole was 0·070 sec., a figure slightly lower than the normal mean, but within the normal range of variation. In this and a second case, varying degrees of block were also observed. Pressure tracings in the right auricle, right ventricle, and brachial artery were recorded and are illustrated in Fig. 14. It is seen that the 3: 1 cycle with its longer ventricular diastolic filling period was followed by a larger pressure rise in the brachial artery and right ventricle than was the 2: 1 cycle with its shorter filling period. The auricular pressure tracings were not influenced by the degree of block, while the brachial artery and right ventricular pressures were dependent on the time at which the QRS fell in relation to isometric relaxation. In addition, it was found that the Q–BA_S time of the weak beat was longer by 0·020 sec. than the Q–BA_S time of the strong beat, if both beats were read at the same pressure levels. This suggests that the duration of isometric contraction was prolonged following poor filling of the ventricles. Similar observations regarding the influence of the varying A-V response upon the brachial artery pressure are seen in Fig. 15 which illustrates a case of auricular flutter with successive 3: 1, 2: 1, 1: 1 A-V ratio.

(5) *Heart Block*

Nine cases with different types of heart block were studied; two cases of complete heart block with idio-

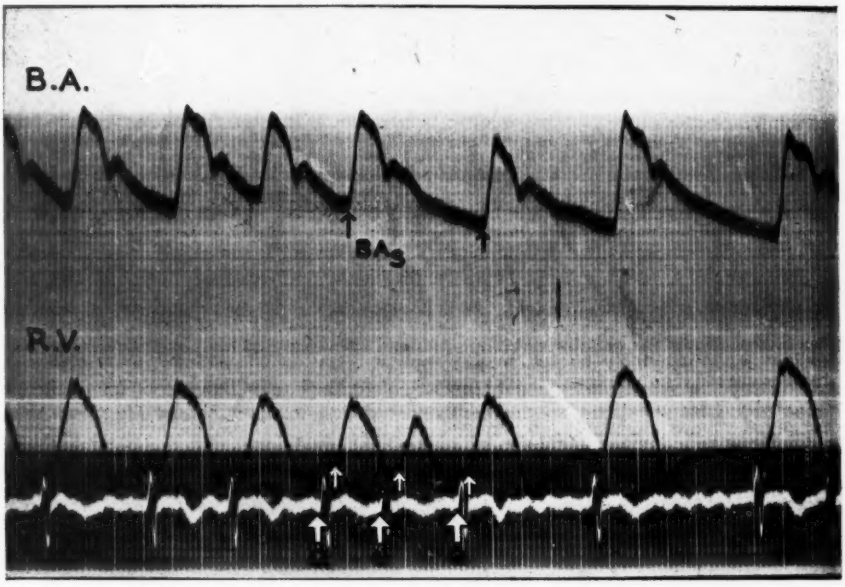

FIG. 12.—Record illustrating electrical-mechanical events in a case of auricular fibrillation.
From top to bottom, blood pressure tracings in the brachial artery (B.A.), right ventricle (R.V.), and electrocardiogram lead II.
In the three beats indicated by arrows the successive Q–RV_S and Q–BA_S times were: first beat, Q–RV_S = 0·110 sec. and Q–BA_S = 0·190 sec.; second beat, Q–RV_S = 0·110 sec. and Q–BA_S not measurable; third beat, Q–RV_S = 0·070 sec. and Q–BA_S = 0·170 sec.

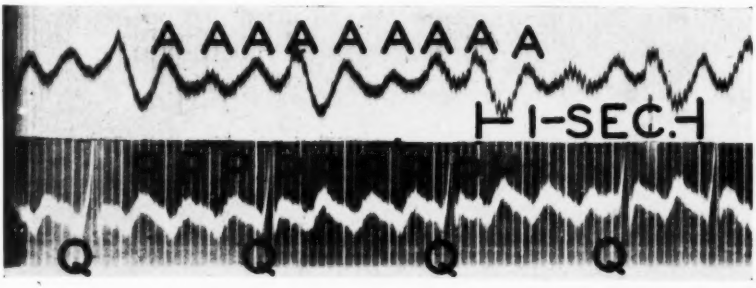

FIG. 13.—Auricular flutter. Record illustrating electrical-mechanical events in a case with a 4: 1 A-V response.
From top to bottom, right atrial blood pressure tracings and electrocardiogram lead II. For discussion see text.

ventricular rhythm originating in the His bundle, one case of incomplete A-V heart block, two cases of left bundle branch block, two cases of right bundle branch block, and two cases of right bundle branch block with 2: 1 A-V heart block, one of which showed runs of complete heart block.

(*a*) *Complete heart block.* The two cases with complete heart block had P waves and QRS complexes of normal duration. The data relating to the duration of the time intervals between electrical and mechanical events will be found in Table VII. As was to be expected, the P–AT_S, the Q–RV_S, and the

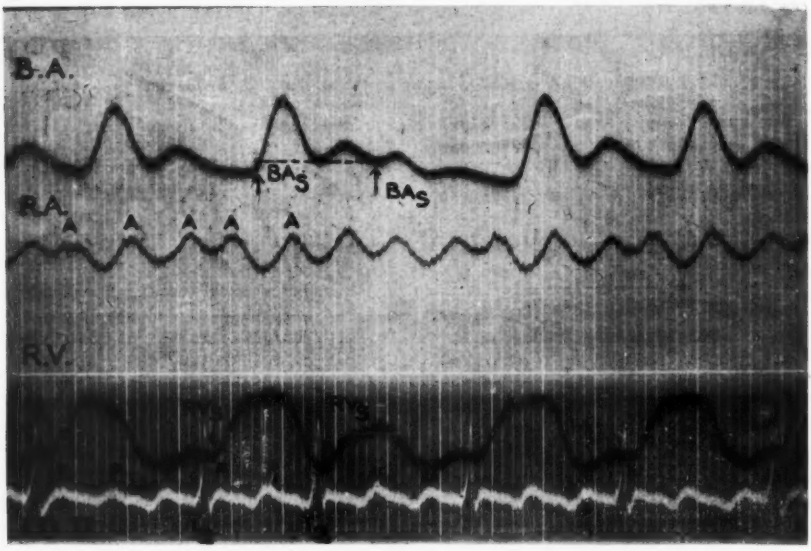

FIG. 14.—Auricular flutter. Record illustrating electrical-mechanical events in a case with 3: 1, 2: 1 A-V response.

From top to bottom, blood pressure tracings in the brachial artery (B.A.), the right atrium (R.A.), the right ventricle (R.V.), and electrocardiogram lead II.

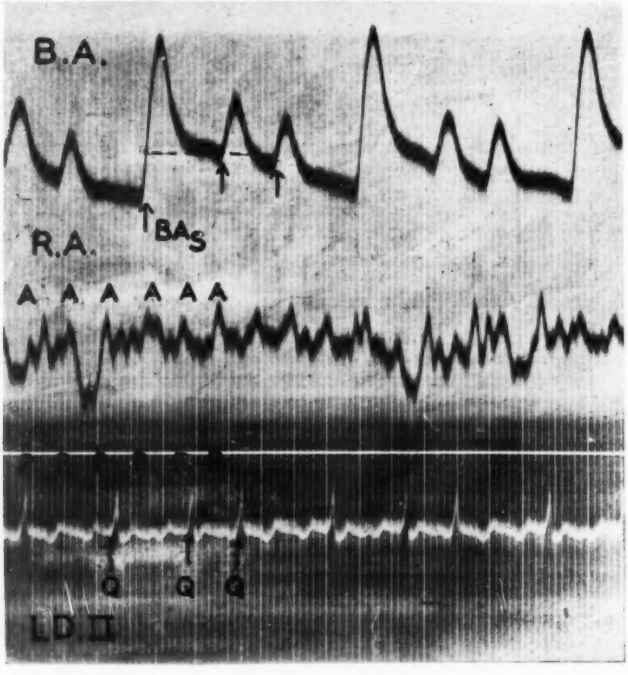

FIG. 15.—Auricular flutter. Record illustrating electrical-mechanical events in a case with 3: 1, 2: 1, 1: 1 A-V ratio.

From top to bottom, blood pressure tracings in the brachial artery (B.A.), the right atrium (R.A.), and electrocardiogram lead II. For discussion see text.

TABLE VII

RELATIONSHIP BETWEEN ELECTRICAL AND MECHANICAL EVENTS IN TWO CASES OF COMPLETE HEART BLOCK

	Case 254	Case 341
Auricular rate per minute	94	86
Ventricular rate per minute	33	33
QRS interval, sec.	0·080	0·090
P–At_S interval, sec.	0·090	0·090
Q–RV_S interval, sec.	0·070	0·070
Q–BA_S interval, sec.	0·140	0·150

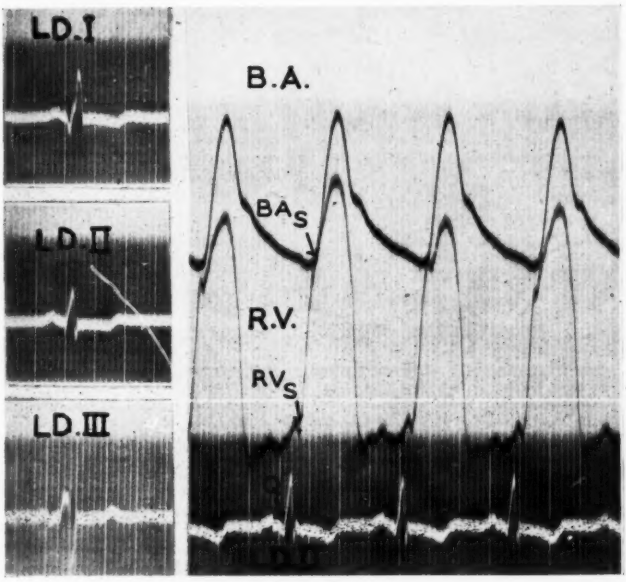

FIG. 16.—Record illustrating electrical-mechanical events in a case with left bundle branch block.

To the left, are the standard leads of the electrocardiogram demonstrating left bundle branch block. Præcordial leads showed delayed peak of R in V5 and V6. To the right, from top to bottom, are blood pressure tracings in the brachial artery (B.A.), the right ventricle (R.V.), and electrocardiogram lead II. For time intervals see Table VIII, Case 416, and for discussion see text.

Q–BA_S times were normal. There was, therefore, no delay and no asynchronism in the pressure build-up of either ventricle. A characteristic tracing of pressure in the right auricle may be seen in Fig. 17. The striking feature was the regular sequence of auricular systoles which occurred at various times in relation to the ventricular cycles. It is seen that the characteristic drop of auricular pressure during ventricular ejection took place at the expected time after the QRS complex. The height of the A wave corresponding to auricular systole was variable, depending on whether or not the ventricle was in systole or diastole, i.e. the tricuspid valve was opened or closed, the largest deflection occurring when the tricuspid valve was closed. (See the first and the last A in lower section of Fig. 17.) In the few instances where a P wave fell approximately 0·12 to 0·20 sec. before the QRS complex, the auricular pressure tracing showed the characteristic deflection of an *a* wave followed by a *c* wave preceding the descent

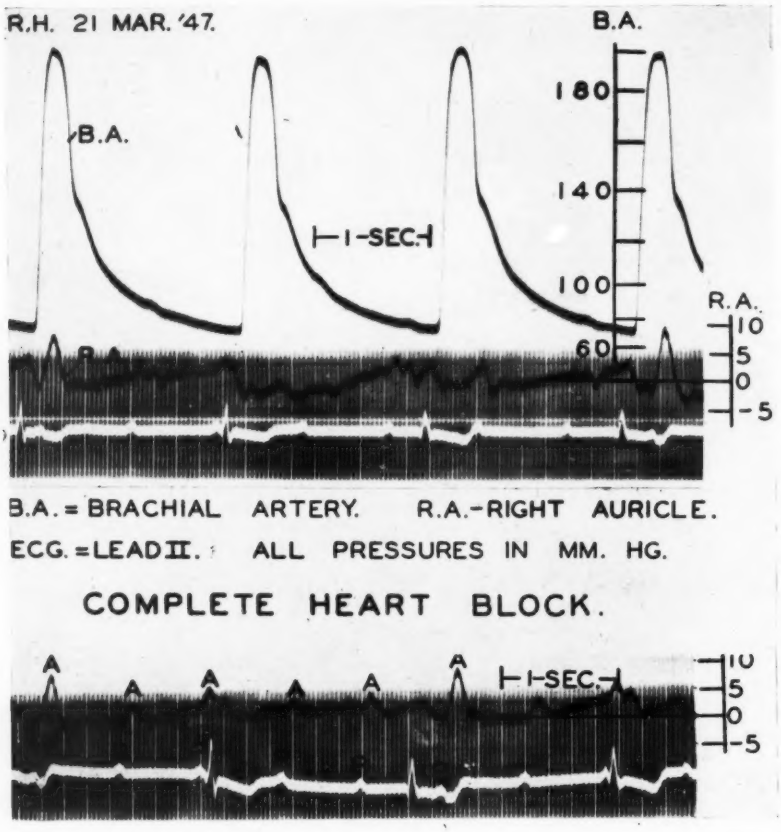

FIG. 17.—Complete heart block. Records illustrating electrical-mechanical events in such a case.

In the upper section from top to bottom, blood pressure tracings in the brachial artery (B.A.), the right atrium (R.A.), and electrocardiogram lead II. In the lower section, blood pressure tracings in the right atrium (R.A.) and electrocardiogram lead II.

of the base. (See the third A from the left in lower section of Fig. 17.)

(*b*) *Incomplete A-V heart block.* Incomplete A-V heart block with prolongation of the PR interval was observed in a patient with generalized scleroderma involving the heart and lungs (Fig. 18). The duration of the P wave was normal and the P–R interval was prolonged to 0·25 sec. The P–AT_S time was lengthened to 0·16 sec., whereas the Q–RV_S and Q–BA_S times were normal, 0·08 sec. and 0·14 to 0·16 sec. respectively. The lengthening of the P–AT_S time suggests that there was abnormality in contraction of the auricle and apparently no difficulty in conduction within the auricular muscle as evidenced by the normal width of the P wave. In a previous publication, Cournand *et al.* (1946), the prolonged Q–RV_S time reported was incorrect as subsequent examination revealed the portion of the tracing read to be damped.

(*c*) *Bundle branch block.* Ventricular asynchronism in the presence of bundle branch block has been demonstrated by several authors, using the peripheral arterial pulse wave or stethogram recorded simultaneously with the electrocardiogram. More complete data pertaining to this type of asynchronism can be added by comparison of the Q–RV_S and Q–BA_S times, since the former gives direct information concerning contraction of the right ventricle and

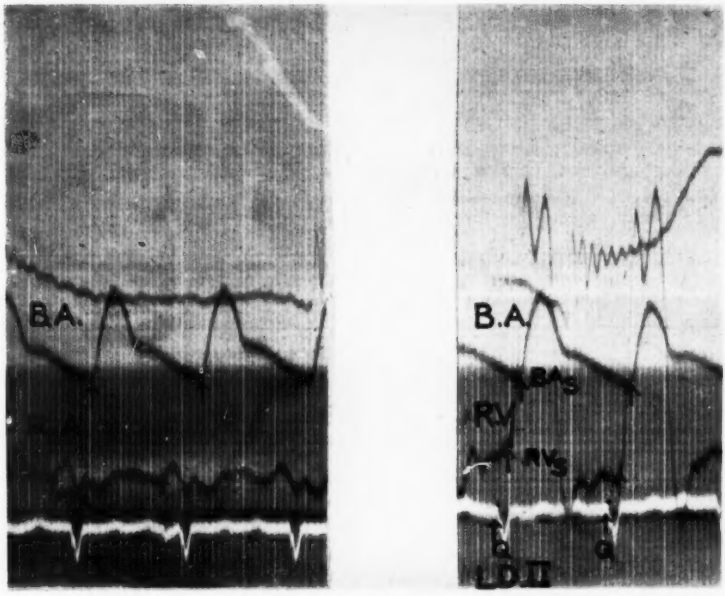

FIG. 18.—Record illustrating electrical-mechanical events in a case with incomplete A-V block (prolonged P–R interval) associated with generalized scleroderma involving the heart and lungs. In the section to the left, from top to bottom, pneumogram, blood pressure tracings from the brachial artery (B.A.), the right atrium (R.A.), and electrocardiogram lead II. In the section to the right, pneumogram, blood pressure tracings from the brachial artery (B.A.), the right ventricle (R.V.), and electrocardiogram lead II. For discussion see text.

the latter indirect information concerning left ventricular contraction.

(i) *Left bundle branch block*. Three patients with hypertensive and arteriosclerotic heart disease, congestive heart failure, and left bundle branch block were studied and the data is presented in Table VIII and one case (416) is illustrated in Fig. 16. The time intervals in the three cases suggest a normal contraction time of the right ventricle and delayed contraction of the left ventricle, consistent with the ventricular asynchronism expected with left bundle branch block.

(ii) *Right bundle branch block*. In two cases, right bundle branch block was induced following the oral administration of 0·80 g. of quinidine sulphate. The electrocardiogram and blood pressure tracings, therefore, could be compared before and after the appearance of the bundle branch block. The data may be found in Table IX. In the first case, a 21 year old girl with an interventricular septal defect,

TABLE VIII

RELATIONSHIP BETWEEN ELECTRICAL AND MECHANICAL EVENTS IN THREE CASES OF LEFT BUNDLE BRANCH BLOCK

	Case 306*	Case 261	Case 416
QRS interval, sec.	0·120	0·160	0·120
Q–RV_S interval, sec.	0·070	0·090	0·090
Q–BA_S interval, sec.		0·220	0·240
Q–FA_S interval, sec.	0·200† and 0·230†		

* A case with pulsus alternans.

† Time interval variation corresponding to strong and weak beats of pulsus alternans (see text).

TABLE IX

RELATIONSHIP BETWEEN ELECTRICAL AND MECHANICAL EVENTS IN RIGHT BUNDLE BRANCH BLOCK

Right Bundle Branch Block induced by Quinidine

	Case 333		Case 351	
	Control	R.B.B.Bl.	Control	R.B.B.Bl.
QRS interval, sec.	0·060	0·120	0·105	0·120
Q–RV_S interval, sec.	0·070	0·110	0·070	0·110
Q–BA_S interval, sec.	0·170	—	0·190	0·190

Right Bundle Branch Block in Cases with Arteriosclerotic Heart Disease and Cor Pulmonale (Case 440) and with 2: 1 A-V Block (Cases 302 and 268)

	Case 440	Case 302	Case 268
QRS interval, sec.	0·140	0·160	0·170
Q–RV_S interval, sec.	0·130	0·120	0·105
Q–PA_S Interval, sec.	0·150	—	—
Q–BA_S interval, sec.	0·130	0·170	0·240

the control tracings showed normal electrical complexes and time intervals. After quinidine, a right bundle branch block developed and the normal Q–RV_S time of 0·070 sec. was prolonged to 0·110 sec. In the second case, a 60 year old man with arteriosclerosis and an old myocardial infarct, the control electrocardiogram showed evidence of myocardial damage and early incomplete bundle branch block, characterized by a QRS of 0·105 sec. in lead II and a delayed peak of the R wave over the left præcordium. Before administration of quinidine, the Q–RV_S time was normal but the Q–BA_S time was slightly prolonged, confirming the electrocardiographic diagnosis of early incomplete left bundle branch block. After quinidine, an S wave appeared in lead I and the QRS complex increased in that lead to 0·120 sec. The Q–BA_S time remained unchanged but the Q–RV_S time increased from 0·070 sec. to 0·110 sec. (Fig. 7). In Fig. 19 (Table IX, Case 440) is illustrated an additional case of right bundle branch block observed in a patient with arteriosclerotic heart disease and cor pulmonale, in which a markedly prolonged Q–RV_S time is seen.

In summary, intracardiac and intra-arterial blood pressure tracings recorded simultaneously with the electrocardiogram demonstrated clearly the presence of ventricular asynchronism in bundle branch block.

These findings confirm and add to the observations of various authors (Castex *et al.*, 1941; Battro *et al.*, 1936; Katz *et al.*, 1927 and 1935; Kossman *et al.*, 1947; Nichol, 1933; and Wolferth *et al.*, 1935) who have studied mechanical and electrical relationships in bundle branch block. Various types of simultaneous tracings were employed by these authors and include electrocardiograms, peripheral artery blood pressure tracings, and in a few instances stethograms, phlebograms, and apical cardiograms. They found that in left bundle branch block there was a prolongation of the "ejection time" which corresponded to the prolongation of the Q–BA_S time found in the present study. In right bundle branch block the "ejection time" remained essentially normal. Data concerning the events in the right ventricle was obtained by indirect means and is subject to interpretation.

(*d*) *Right bundle branch block with incomplete* 2: 1 *A-V block*. In 2 patients a 2: 1 A-V block was associated with right bundle branch block. In addition, one of these patients had short periods of complete heart block. The data in these two cases may be found in Table IX. In the first case the duration of the QRS complex was 0·160 sec., the ventricular complexes were of the aberrant type with downward deflection in lead I and upward deflection in lead III, suggesting that the stimulation arrived first in the left ventricle. The Q–RV_S time was significantly prolonged to 0·120 sec. while the Q–BA_S time was normal (0·170 sec.).

In the second case (Fig. 20 and 21 and Table IX, Case 268) during the periods of incomplete 2: 1 heart block the P–R interval was markedly prolonged to 0·310 sec. The Q–RV_S and Q–BA_S times were both lengthened to 0·105 and 0·240 sec., respectively. During the period of complete heart block with an auricular rate of 71 and a ventricular rate of 27, the ventricular complexes were of the same aberrant configuration and the same duration, again with downward deflection in lead I, upward in lead III.

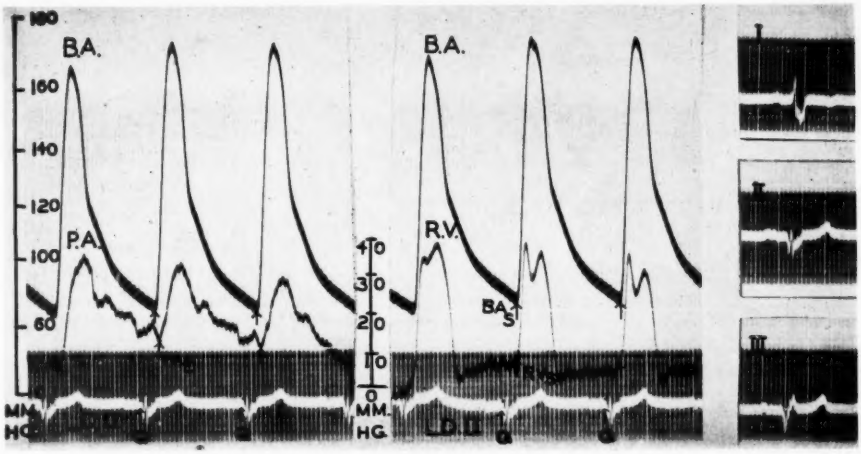

FIG. 19.—Records illustrating electrical-mechanical events in a case with right bundle branch block. To the right, are the standard leads of the electrocardiogram demonstrating right bundle branch block. In the centre, are blood pressure tracings in the brachial artery (B.A.), the right ventricle (R.V.), and electrocardiogram lead II. To the left, are blood pressure tracings in the brachial artery (B.A.), the pulmonary artery (P.A.), and electrocardiogram lead II.

Note, as in Fig. 3, the ascending slopes of the right ventricle and pulmonary artery do not coincide. For figures see Table IX, Case 440. For discussion see text.

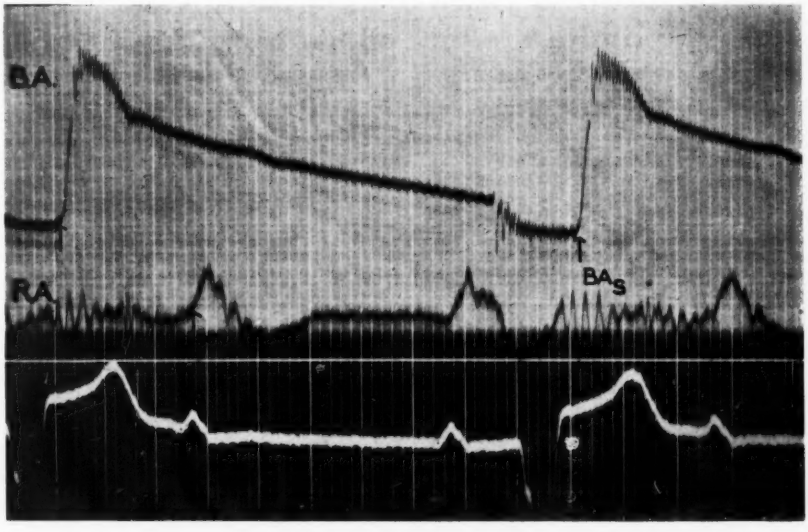

FIG. 20.—Records illustrating electrical-mechanical events in a case with right bundle branch block and 2: 1 A-V block.

From top to bottom, blood pressure tracings in the brachial artery (B.A.), the right atrium (R.A.), and electrocardiogram lead II.

For data see Table IX, Case 268, and for discussion see text.

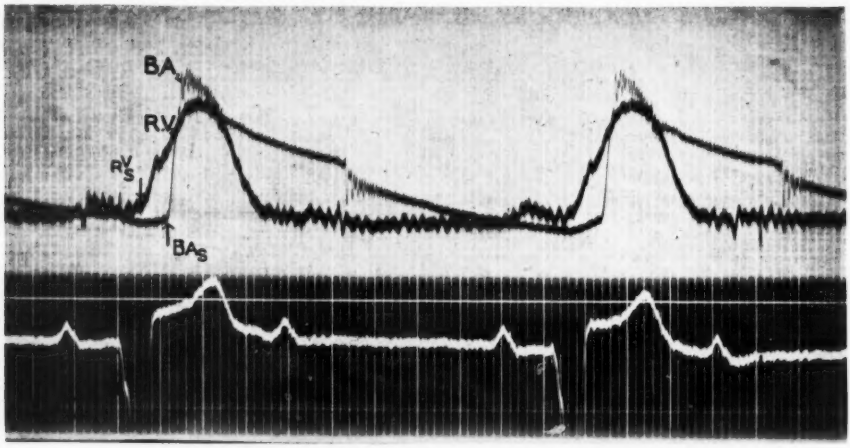

FIG. 21.—Records illustrating electrical-mechanical events in a case with right bundle branch block and 2: 1 A-V block.

From top to bottom, blood pressure tracings in the brachial artery (B.A.), the right ventricle (R.V.), and electrocardiogram lead II.

For data see Table IX, Case 268, and for discussion see text.

This suggests that ventricular depolarization was the same as during incomplete A-V block, and that the idioventricular focus was probably in the His bundle. The $Q–RV_s$ and $Q–BA_s$ time intervals were unchanged. During both complete and incomplete A-V block the duration of $P–AT_s$ time was short (0·050 sec.), see Fig. 20, indicating no abnormality of auricular contraction, in contrast to the findings in the case with incomplete A-V block previously described.

These two patients are of particular interest because during a period of 2: 1 block with right bundle branch block the electrocardiographic patterns were identical. In the first case there was a delay in right ventricular contraction, whereas in the second case slow spread of stimulation or delay in contraction existed in both ventricles.

(6) *Pulsus Alternans*

One case of hypertensive and arteriosclerotic heart disease with left bundle branch block showed evidence of pulsus alternans of the mechanical type. The findings in this case (306) are illustrated in Fig. 22 and the data listed in Tables VIII and X. In the femoral artery tracings there was a variation in the systolic peak which occurred in a regular manner and may be interpreted as a succession of strong and weak beats. In contrast there was a steady level of the systolic peaks in the right ventricle. There was no evidence in the electrocardiogram of electrical alternation. The duration of the QRS complex in alternate beats remained the same and the $Q–RV_s$ time also did not vary. The striking abnormality was the rhythmic variation of the $Q–BA_s$ time. This interval was shorter for the beat corresponding to the high systolic peak and longer for the beat corresponding to the lower systolic peak. These variations in pressure as well as the variations in the $Q–BA_s$ time, occurring rhythmically without any variation in the duration of the QRS complex, suggest a less efficient ventricular contraction every other beat. However, it is not possible to eliminate

TABLE X

RELATIONSHIP BETWEEN ELECTRICAL AND MECHANICAL EVENTS IN PATIENT WITH PULSUS ALTERNANS (CASE 306)

	Strong beat	Weak beat
QRS interval, sec.	0·120	0·120
$Q–RV_s$ interval, sec.	0·070	0·070
$Q–FA_s$ interval, sec.	0·200	0·230

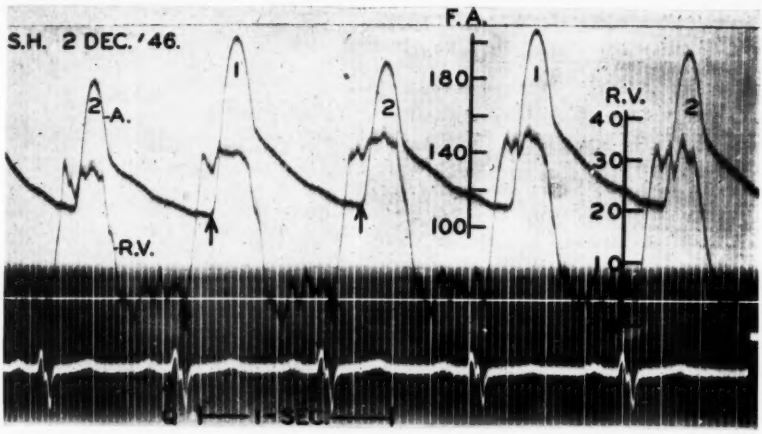

FIG. 22.—Pulsus alternans. Records illustrating electrical-mechanical events in such a case. From top to bottom, blood pressure tracings in the femoral artery, the right ventricle, and electrocardiogram lead II. No. 1 corresponds to the strong beat and No. 2 to the weak beat.

Note absence of alternation of pressure in right ventricle. For data see Tables VIII and X, Case 306, and for discussion see text.

F.A. = Femoral artery. R.V. = Right ventricle. All pressures in mm. Hg. Electrocardiogram, lead II.

as a factor rhythmic variation of peripheral vascular tone of reflex origin, which would ultimately influence the curve of blood ejection from the left ventricle into the aorta and the pulse wave velocity.

SUMMARY AND CONCLUSIONS

The relationship between electrical and mechanical events in the cardiac cycle was studied in normal subjects, in children with congenital heart disease, and in adults with cardiovascular disease.

In children the intervals were shorter than those of normal adults. The prolongation of the isometric contraction of the right ventricle in children with congenital heart disease seemed to be dependent upon hypertension of the lesser circulation.

In adults with heart disease who had normal sinus rhythm and no conduction abnormalities, the time intervals were identical with those found in normal adults unless they were in congestive failure with hypertension of the lesser circulation. In this event the $Q–PA_s$ time interval was slightly prolonged and the duration of isometric contraction of the right ventricle was also longer than normal.

Abnormalities of rhythm, conduction, and contraction encountered in patients with cardiovascular disease were also analysed and the following points deserve emphasis.

(*a*) Ventricular premature contractions apparently produce two types of asynchronism with a lag in one or the other ventricle. It is difficult to interpret the relationship between electrical configuration of the premature contractions and the mechanical events, since premature beats with electrocardiographic patterns identifying them as arising from opposite ventricles produced the same type of ventricular asynchronism.

(*b*) In chronic auricular fibrillation, in addition to the complete arrhythmia, disturbances of the contraction mechanism of both ventricles were present.

(*c*) In auricular flutter the time intervals remained constant and normal during pure flutter with a constant A-V ratio. Minor variations in the $Q–RV_s$ and $Q–BA_s$ intervals as well as variations in right ventricular and brachial artery systolic pressures were found when the degree of block varied.

(*d*) In cases of complete heart block with bundle of His ventricular rhythm the auricular and ventricular electrical-mechanical intervals remained normal even though the conduction defect consisted of complete A-V dissociation. In uncomplicated bundle branch block ventricular asynchronism of the expected type was found. However, in one patient with both incomplete 2:1 A-V block and right bundle branch block there was a delay in onset of the mechanical systole in both ventricles.

Acknowledgment is made of the assistance of H. L. Motley, D. T. Dresdale, H. M. Weiner, and A. Himmelstein, in the recording of blood pressure tracings.

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R WAVES INTERRUPTING T WAVES

BY

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In the course of some experiments on anæsthetized dogs and cats concerned with the production experimentally of ventricular flutter and ventricular fibrillation, Fastier and Smirk (1948) noted that R waves sometimes appeared on the descent of the antecedent T waves, shortly before the onset of ventricular flutter. The flutter was induced by a substance amarin * which had been found by one of us (F.H.S.) to alter the response of the animals to adrenaline so that a moderate dose of adrenaline, ordinarily well tolerated, would now give rise to ventricular flutter.

These observations led me to seek more closely for such phenomena in human electrocardiograms. The present paper concerns 17 patients in whom R waves have been observed on the T waves of antecedent complexes. It seems that interruptions of T waves by R waves are not very uncommon, are likely to prove important prognostically, and seem to provide an indication for treatment.

Little has been written on this subject either from the experimental or from the clinical standpoint, and such information as is available may be unfamiliar to some of the authors who have published records without commenting upon the phenomenon. The first reference I was able to discover to the occurrence of an R wave on a T wave was in a footnote by Katz (1928) in the course of his comprehensive review on the T wave. Katz mentioned here that an example of an R wave on a T wave has been observed by Dr. Ashman, three examples by Drs. Feil and Seigel, and three by himself. He mentioned that the only published record was by Wenkebach and Winterberg (1927) and that Wiggers had seen it in dogs. I have been unable to find any record of subsequent reports on the finding of R waves on the T waves with the exception of Scherf and Boyd (1940) and of Ashman and Hull (1941) in their books on electrocardiography; they confine themselves to the statement that an R wave may encroach on the descent of the T wave.

The published electrocardiograms show many examples in which R waves appear to arise on the descent of T waves but, with the exception referred to above, I have found so far no corresponding comment by the authors.

Theoretically R waves might occur superimposed upon T waves in several ways. Most of these theoretical possibilities have been given practical illustration in the 17 cases here reported.

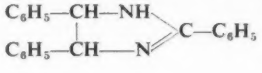
(1) A ventricular complex of supraventricular origin could be interrupted by another ventricular complex of supraventricular origin (Cases 3, 4, 13, 14, 15, 16; Fig. 3 and 9). This might occur in auricular paroxysmal tachycardia in auricular fibrillation (Fig. 3 and 9), in auricular flutter, and possibly with very premature auricular systoles.

(2) A ventricular complex of supraventricular origin could be interrupted by a premature ventricular complex (Cases 1, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15, 17; Fig. 6 and 7).

(3) A premature ventricular complex could be interrupted by a ventricular complex of supraventricular origin (Case 4; Fig. 4).

(4) A premature ventricular complex could be interrupted by another premature ventricular complex (Cases 1, 2, 4, 5, 7, 8; Fig. 1, 2, 4, 5, and 8). This last might occur with single pairs of ventricular premature beats (Fig. 1) or in the course of ventricular paroxysmal tachycardia (Fig. 2).

Reference to published cardiographic tracings illustrating a variety of cardiological conditions suggests that some of the other theoretical possibilities may have been realized. For example interruptions of paroxysmal auricular tachycardia (Graybiel and White, 1946) in which the P waves appeared in the S–T segments.

* 

Case Reports

Case 1, male, aged 59 years. Retrosternal pain twelve hours before admission. The electrocardiographic diagnosis was that of *anterior apical infarction*. In two instances in about 46 seconds of electrocardiographic recording examples were found of an ectopic ventricular complex interrupted before its completion by a subsequent ectopic complex (Fig. 1). Both interruptions occurred on the latter half of the T wave.

The patient was improving during the first 19 days and then had an extension of the cardiac infarction with a further fall in the blood pressure. Next day he was noticed to be breathing stertorously. Shortly after he tried to sit up and died suddenly, as was thought, from ventricular flutter. The autopsy revealed multiple small infarcted areas in the anterior apical region.

Case 2, male, aged 46 years. *Cardiac infarction*. Severe retro-sternal pain of 36 hours duration. About one month after admission the patient developed a *ventricular paroxysmal tachycardia* and was treated by quinidine which restored a natural regular rhythm. The patient was discharged in good condition.

The electrocardiograms were indefinite in regard to the clinical diagnosis of cardiac infarction. The terminal deflection of the first run of tachycardia

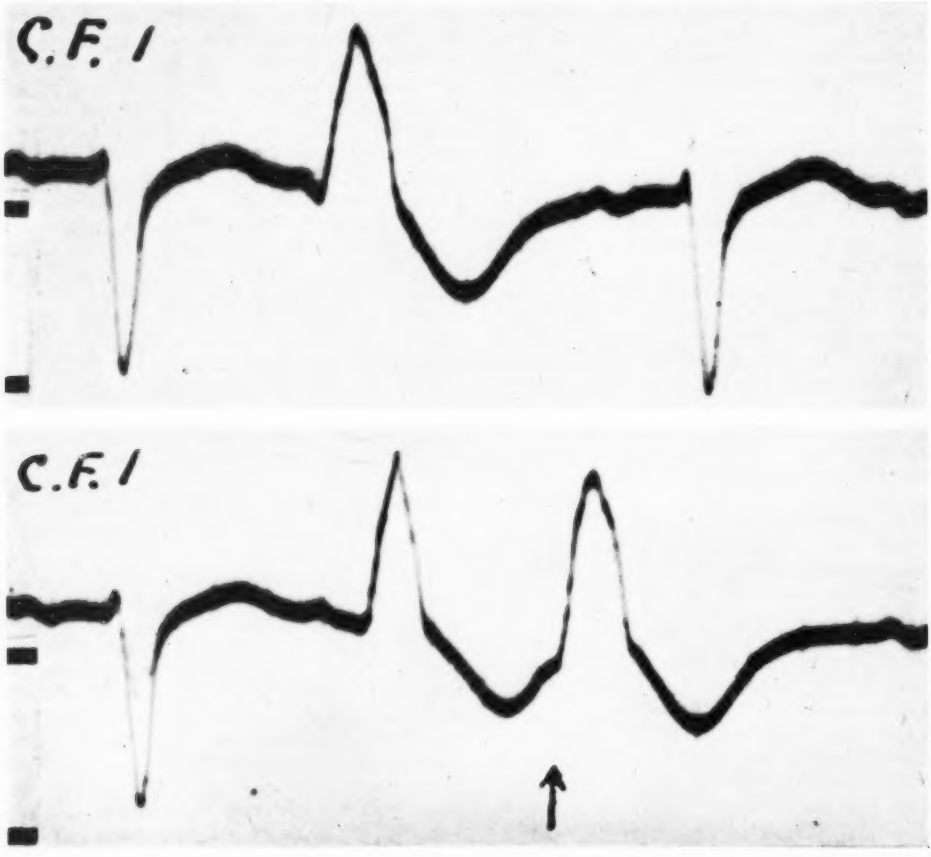


Fig. 1.—Case 1. The upper trace shows a single uninterrupted premature ventricular systole and the lower shows a pair of premature ventricular systoles of which the second interrupts the terminal deflection of the first. The interrupted complex may be compared in shape with the complete complex in the upper trace and with the complex that follows it. Time intervals 0·1 sec.

in lead III and the ventricular complex towards the end of the lead III strip indicate the shape and duration of uninterrupted ventricular complexes (Fig. 2). In the middle of the paroxysm the individual complexes differ in duration and this seems to depend chiefly on the point at which the T-like terminal

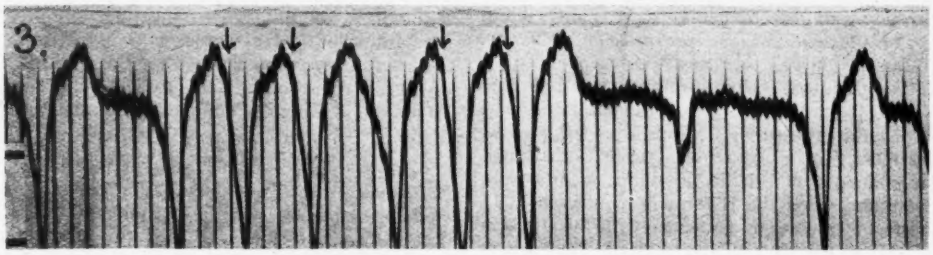


FIG. 2.—Case 2. The trace shows a paroxysm of ventricular tachycardia. This complex at the end of the paroxysm and the complexes at the extreme left and right of the trace are uninterrupted. The arrows mark the points where complexes are interrupted during the paroxysm. Comparison with intact complexes indicates how much of the interrupted complexes have been cut off by the beginnings of new ventricular complexes. Time intervals 0·05 sec.

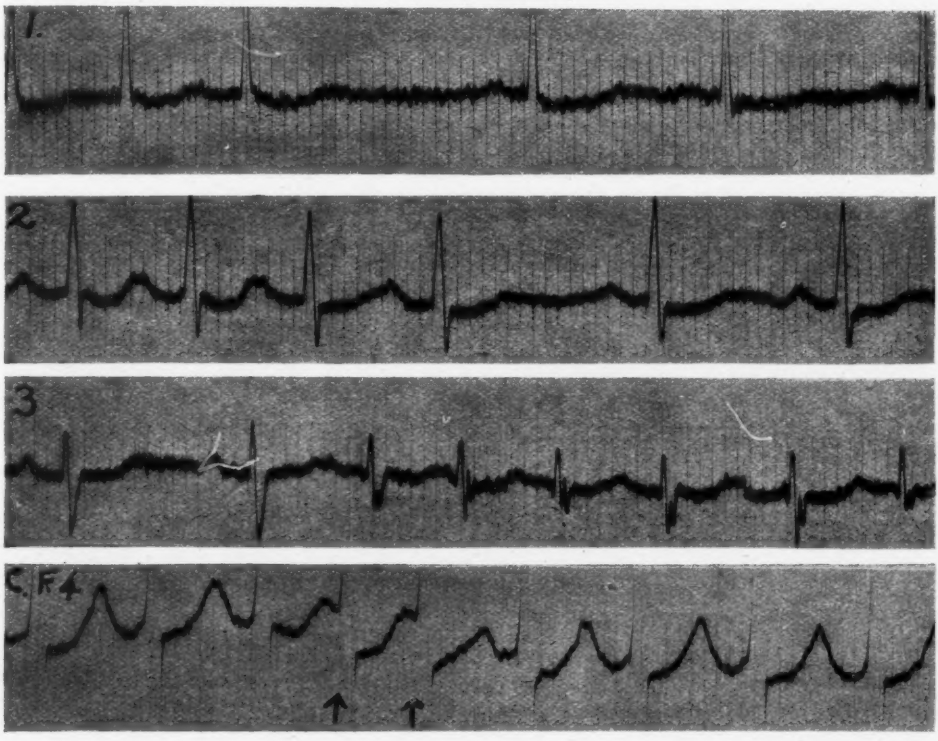


FIG. 3.—Case 3. Lead I shows the end of a period of rapid beating with the return of sinus rhythm, lead II shows an end of rapid beating and lead III the beginning of rapid beating with polymorphic ventricular complexes of supraventricular origin. The irregular arrhythmia has been called paroxysmal auricular fibrillation. CF4 shows two interruptions by R waves of the antecedent T waves. Time intervals 0·05 sec.

deflection of a complex is interrupted by the initial sharp downward deflection of the next complex.

Case 3, male, aged 56 years. *Myocardial degeneration and thyrotoxicosis. Paroxysmal supraventricular tachycardia probably auricular fibrillation.* Admitted with breathlessness on exertion, of 6 months' duration. Thyroidectomy was followed by improvement in the physical condition. The basic rhythm is regular and of sinus origin. At times there is an irregular tachycardia with ventricular complexes which do not differ greatly from those found when the rhythm is regular (Fig. 3). The irregular rhythm is associated with variations in the shape of the ventricular complexes which, however, are supraventricular in origin. It is not possible entirely to eliminate multiple premature auricular systoles as a cause for the tachycardia but auricular fibrillation seems more likely.

Case 4, male, aged 71 years. *Myocardial degeneration, auricular fibrillation, multiple premature ventricular systoles.* Admitted to hospital because of a confused mental state. He was reasonably active for his years. Irregular rhythm due to auricular fibrillation and short runs of paroxysmal ventricular tachycardia. Interruptions of T waves by R waves occur frequently. Some of these are interruptions of ventricular complexes of supraventricular origin by premature ventricular complexes, others are of premature ventricular complexes by other premature ventricular complexes (Fig. 4A). Instances were observed of the interruption of a premature ventricular complex by a ventricular complex of supraventricular origin (Fig. 4 A and B) and of a ventricular complex of supraventricular origin by another ventricular complex of supraventricular origin.

Case 5, male, aged 71 years. *Myocardial degeneration, auricular bigeminy, sinus bigeminy, multiple premature ventricular systoles.* Admitted because of a right-sided inguinal hernia and found to have cardiac irregularity. In the last four months before admission there had been shortness of breath on exertion but no swelling of the ankles. (See Fig. 5.)

Case 6, male, aged 58 years. *Cardiac infarction.* Electrocardiograms showed a cardiac infarction and multiple premature ventricular systoles with interruptions of T waves by R waves (Fig. 6).

Case 7, female, aged 40 years. *Myocardial damage of unknown origin, multiple premature systoles.* Numerous examples of ventricular premature systoles interrupting beats of normal sinus origin

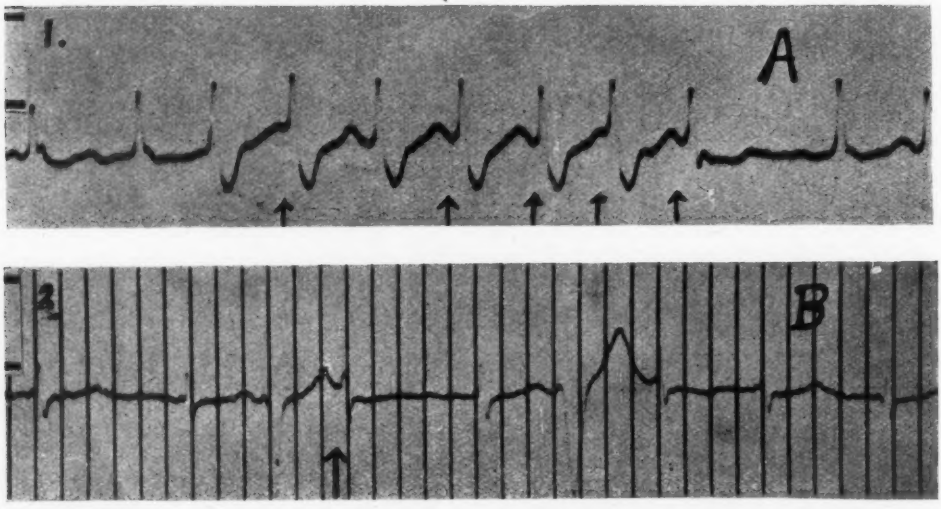


FIG. 4.—Case 4.
(A) Auricular fibrillation. The trace shows a run of six premature ventricular systoles followed by what appears to be a ventricular complex of supraventricular origin interrupting the T wave of the last premature ventricular systole.
(B) Auricular fibrillation. The trace shows the T wave of a premature ventricular complex interrupted by a ventricular complex which is clearly of supraventricular origin. Time intervals 0·1 sec.

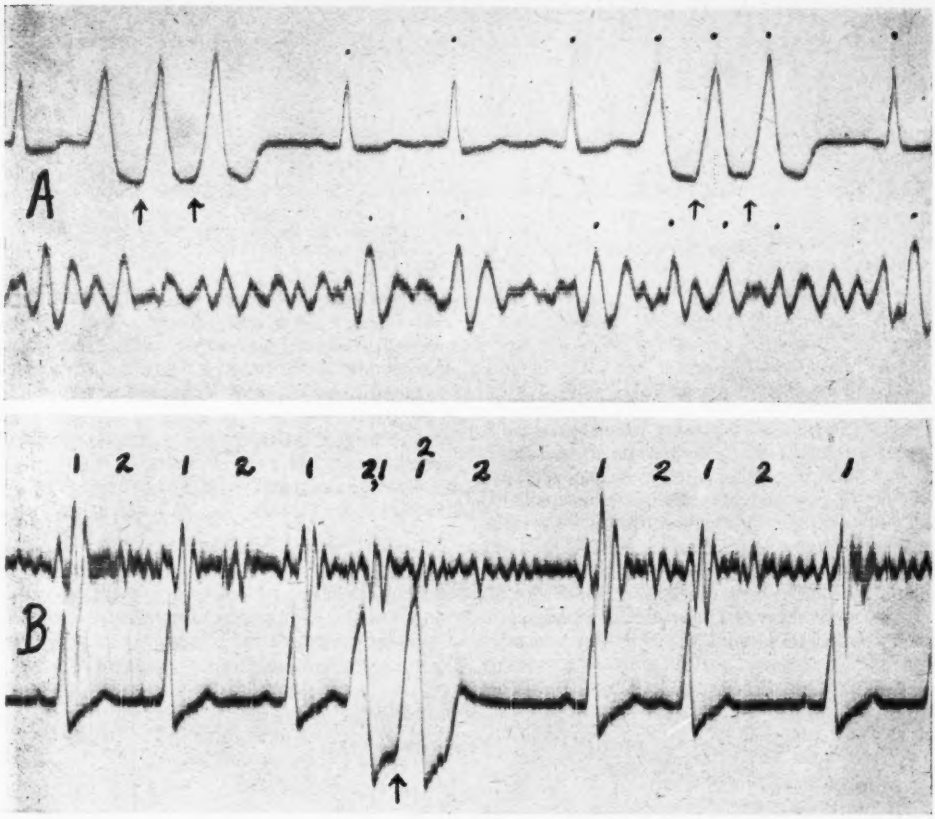


FIG. 5.—Case 5.

(A) The upper trace is an electrocardiogram recorded by a Matthews' oscillograph and shows auricular bigeminy broken by premature ventricular systoles which occur in two groups, each of three ventricular complexes. The 1st and 2nd premature ventricular systoles in each group are interrupted respectively by the 2nd and 3rd premature ventricular systoles. The shape of the uninterrupted 3rd systoles shows that the 1st and 2nd systoles are incomplete. The ballistocardiographic trace, using Malcolm's instrument, indicates a much smaller output of the heart from the premature than from natural systoles. Time trace 0·2 sec.

(B) The lower trace is a heart sound record and the lower trace a simultaneous lead II electrocardiagram, both taken using a pair of Matthews' oscillographs. The latter shows a supraventricular bigeminy with wandering pacemaker and two premature ventricular systoles of which the second interrupts the first. The heart sounds alternate in intensity during the bigeminy, the louder sound following the longer diastole. The premature ventricular systoles give rise to weaker heart sounds. The second premature systole leads to a second heart sound. This raises the question of whether some filling of the heart took place between the two premature ventricular beats. Time trace 0·2 sec.

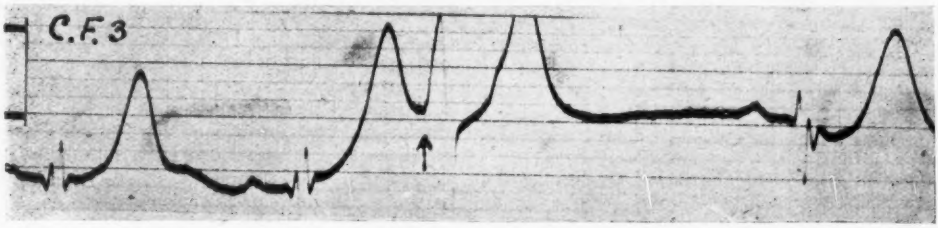


FIG. 6.—Case 6. The trace shows the interruption of a complex of sinus origin by a ventricular premature systole at the point marked with an arrow. Time intervals 0·05 sec.

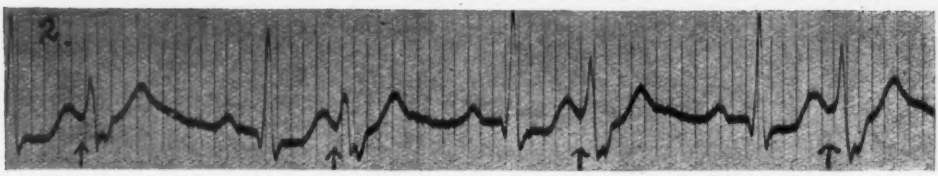


FIG. 7.—Case 7. The trace shows interruptions of the T waves of complexes of sinus origin by the R waves of premature ventricular systoles. Time intervals 0·1 sec.

(Fig. 7). Examples were also encountered of polymorphic ventricular premature systoles interrupting other premature ventricular systoles. Apart from the numerous premature beats the electrocardiogram would have passed as normal.

Case 8, male, aged 77 years. *Cardiac asthma, general congestive heart failure, benign arterial hypertension.* Shortness of breath on exertion for two years, swelling of the ankles for one month, and extreme nocturnal breathlessness for four days prior to admission. The blood pressure was 220/108. The basic rhythm, of sinus origin, was interrupted by frequent polymorphic premature ventricular systoles occurring at various times after the antecedent complexes. Interruptions of T waves by R waves were frequent (Fig. 8).

Case 11, male, aged 79 years. *Recent cardiac infarction.* This patient began with vomiting, and pain in the chest. He was obviously very ill and cyanosed, his condition deteriorated and he died. Cardiograms show a basic sinus rhythm with normal P–R interval interrupted by numerous premature

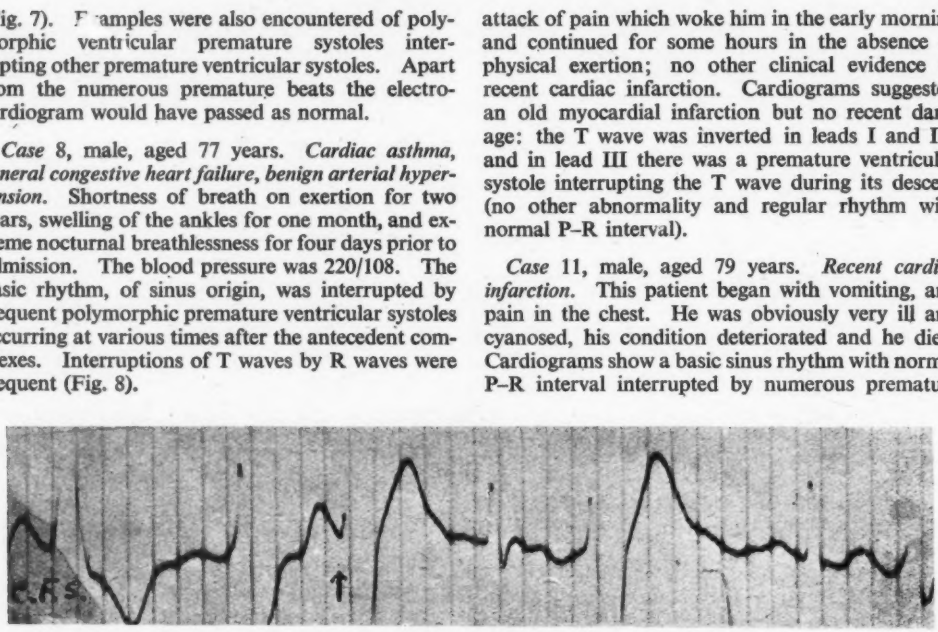


FIG. 8.—Case 8. The trace shows interruption of the terminal deflection of an ectopic ventricular complex by the initial deflection of another ectopic ventricular complex. Time intervals 0·1 sec.

Case 9, male, aged 63 years. *Posterior basal infarct.* One month after the onset of the infarction, the patient, apparently well on the way to recovery, was telling the ward sister how well he felt and suddenly dropped back dead, apparently from ventricular flutter or fibrillation. The autopsy revealed a posterior basal cardiac infarction. Cardiograms showed interruption of ventricular complexes of supraventricular origin by ectopic ventricular complexes. The premature beats occurred at varying intervals after the previous beats but were not polymorphic.

Case 10, male, aged 77 years. *Angina of effort, old cardiac infarction.* Admitted because of an attack of pain which woke him in the early morning and continued for some hours in the absence of physical exertion; no other clinical evidence of recent cardiac infarction. Cardiograms suggested an old myocardial infarction but no recent damage: the T wave was inverted in leads I and IV, and in lead III there was a premature ventricular systole interrupting the T wave during its descent (no other abnormality and regular rhythm with normal P–R interval).

ventricular systoles. The QRS–T complexes were approximately 0·1 sec. in duration. There was a 6 mm. Q wave in lead III with a sharply inverted T wave. A clear interruption of the T wave of a complex of sinus origin by an ectopic ventricular complex occurred in lead I.

Case 12, male, aged 77 years. *Myocardial degeneration.* Short of breath and unable to hurry on level ground for six years prior to admission. Signs of congestive heart failure were minimal. Sinus rhythm, but premature ventricular systoles occurred at fairly frequent intervals and several quite distinct interruptions of complexes of supraventricular origin by ectopic ventricular complexes occur.

Case 13, female, aged 78 years. *Cardiac asthma, auricular fibrillation, hypostatic pneumonia.* Admitted with severe breathlessness which was thought to be the result of cardiac asthma. In hospital she developed a hypostatic pneumonia and died. Auricular fibrillation: QRS–T complexes of supraventricular origin sometimes occurred sufficiently early to interrupt the antecedent T wave of other supraventricular complexes about half-way down their descents.

Case 14, female, aged 70 years. *Acute exacerbation of chronic bronchitis, congestive heart failure, auricular fibrillation.* The blood pressure was 180/80. The congestive failure was treated by digitalis, the bronchitis improved, and the patient was discharged in fair condition. Auricular fibrillation: in CF2 and CF4 distinct interruptions of complexes of supraventricular origin by other complexes of supraventricular origin occurred. There was great variation in the shape of the ventricular complexes.

Case 15, female, aged 73 years. *Auricular fibrillation.* Auricular fibrillation and interference with conduction in the branch bundles. Complexes of supraventricular origin were interrupted on occasion by other complexes of supraventricular origin and at times by ectopic ventricular complexes.

Case 16, female, aged 66 years. *Paroxysmal auricular fibrillation.* In two instances R waves were present on the descent of the antecedent T waves (Fig. 9). The QRS–T complexes showed variations in shape. There were no premature ventricular systoles.

Case 17, female, aged 62. *Melancholia, multiple premature systoles.* Admitted for electrical convulsive therapy on account of mental depression, hallucinations, and delusions. Electrocardiograms showed a basic sinus rhythm; the ectopic ventricular complexes were polymorphic but falling, in regard to shape, into two main types of which one type only gave rise to interruptions of the T waves of sinus beats.

Findings in these Cases

The principal features of the 17 cases recorded with R waves interrupting T waves are set out in Table I. Most patients were in the later years of life, ten being over 70 and seven between 40 and 69. There was a preponderance of males. Thirteen exhibited premature ventricular systoles; in one of these, only a single premature ventricular systole was present in the short length of tracing available; in the remaining 12 two or more ventricular premature systoles occurred, in tracings taken with the same lead, and the premature beats were polymorphic in 11 cases (Fig. 7 and 8). Of these 12 cases, 11 showed premature beats starting at irregular intervals of time after the antecedent normal beats. In the remaining case there were only two premature ventricular complexes and a conclusion as to whether the time interval was constant or variable could not be reached. Of the 12 cases with more than one premature systole 8 showed examples of pairs of premature beats occurring together. Some of these showed groups of three together and 3 of the 8 showed runs of paroxysmal tachycardia of five or more complexes (Fig. 2). In two of the cases where no such pairing of the ventricular premature systoles was discovered a considerable length of tracing was available and it seems likely that pairing of the beats was not occurring in these cases. In the other two cases only short lengths of tracing were available and pairing may or may not have been present at other times.

There were six cases with auricular fibrillation and it is interesting that all six showed polymorphic ventricular complexes of supraventricular origin

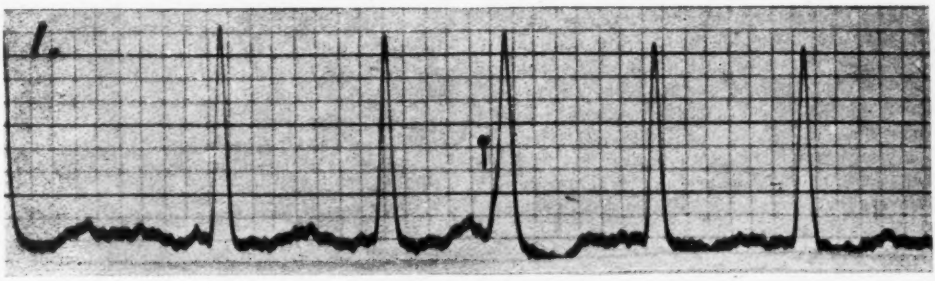


Fig. 9.—Case 16. Auricular fibrillation. T wave interruption. Time intervals 0·05 sec.

(Fig. 3). This polymorphism is not usual in ordinary cases of auricular fibrillation and would appear to be a feature of cases in which R waves appear upon T waves. Two of the six cases with auricular fibrillation also exhibited ectopic ventricular systoles and these also exhibited polymorphism. It was noted, but only when finally analysing the results, that three out of the six cases with auricular fibrillation (Fig. 3) sometimes showed sinus rhythm; this seems to be a higher proportion of paroxysmal auricular fibrillation than one would expect to encounter in a random collection of auricular fibrillation cases. From the above paragraphs it will be seen that in the 16 cases where it was possible to examine the phenomenon, polymorphism occurred in 15, being manifest either in ectopic ventricular complexes or in ventricular complexes of supraventricular origin or in both of these.

The four types of interruption that should occur theoretically have been found in the present series. Five patients were found in whom ventricular complexes of supraventricular origin interrupted other ventricular complexes of supraventricular origin and in one additional patient this probably occurred. These were also patients with auricular fibrillation and no such interruption occurred in any of the patients with sinus rhythm. Interruption of ventricular complexes of supraventricular origin by ectopic ventricular complexes (Fig. 6) and of ectopic ventricular complexes by other ectopic ventricular complexes (Fig. 1 and 4) both occurred fairly frequently, there being 9 patients who definitely, and three more who probably, exhibited the former phenomenon, and six patients who definitely exhibited the latter. Only one patient showed ectopic ventricular complexes being interrupted by ventricular complexes of supraventricular origin (Fig. 4) and this, as might be expected, was in a patient with both auricular fibrillation and multiple ectopic ventricular systoles.

One patient exhibited four types of interruption. Two patients exhibited two kinds of interruption and three patients probably had two types of interruption.

Evidence of Interruption of T Waves by R Waves

Some examples of the interruption of T waves by R waves have been presented. It may be considered that there has been an unmistakable interruption when a ventricular complex of well-defined shape has its latter end cut off by the premature development of an R wave. In most cases complete ventricular complexes can be discovered which, up to the point of interruption, are identical with the interrupted complex, and a comparison of the complete and interrupted complexes makes it quite clear that there has been an interruption (Fig. 1). The distance between the R wave of the interrupted complex and the R wave of the interrupting complex, ordinarily, will be less than the length of the complete QRS–T complex. In patients who show the more striking interruptions of T waves by R waves there are usually in addition a large number of interruptions which, however, are not so convincing—those where the R wave arises low down on the descent of the T wave, those where extracardiac potentials by deflecting the isoelectric base line are altering the shape of the complexes, and those where the interruption appears to be due to a prolongation of the interrupted QRS–T complex as much as to prematurity of the R wave.

Other Features of Cases R Waves on T Waves

Several of the examples of R waves on T waves have been encountered in cases of cardiac infarction especially about the end of the first week and the interruptions then are caused by premature ventricular systoles (Fig. 1 and 6).

In cases which are not cardiac infarctions a variety of clinical conditions have been associated with the appearance of R waves on T waves. Most of these patients show evidence of substantial myocardial damage. In addition, there is a similarity in the electrocardiographic features of all these cases which is not merely accidental.

(1) In 11 out of 12 cases, the ectopic ventricular complexes show variations in the shape (polymorphism). These variations in shape, however, are encountered not only when the premature ventricular systoles arise, as is usual in these patients, from multiple ectopic foci but also among ventricular complexes which arise in response to stimuli of supraventricular origin (Fig. 3).

(2) Ectopic ventricular beats often occur in pairs or triplets or in runs of ventricular paroxysmal tachycardia.

(3) The distances between premature beats and their antecedent normal complexes were variable. When pairs of ventricular premature systoles occur together, the distance between the two members of a pair is also a variable.

As will be seen later, the above changes may indicate increased excitability of the myocardium.

The recognition of the fact that cases exhibiting interruptions of T waves by R waves commonly showed the above features, has led to a more careful, and often fruitful, search for interruptions, more particularly in cases where (*a*) ventricular complexes are polymorphic and at variable intervals after the antecedent beat, (*b*) the heart rate is fast and

irregular, and (*c*) where some of the R waves arise close to the descending limb of the T wave.*

The Refractory Period of Cardiac Muscle

The presence of R waves on T waves indicates that a new wave of excitation may arise within the heart before the previous wave of excitation has ended. This statement has reference to the heart as a whole and in certain cases at least the termination of the T wave does not represent the passing off of the wave of excitation throughout the entire heart. For example, in the case of a left ventricular premature systole, the right side of the heart is the last part to be excited and the terminal part of the T wave represents the passing off of the wave of excitation from the right side. It is not so easy to explain the interruption of the T waves of a supraventricular complex in this way for then, apart from branch bundle block, the T wave represents the passing off of the wave of excitation on both sides of the heart. Such arguments do not go much further than indicating that we cannot eliminate the possibility that a single cardiac muscle fibre may be capable of responding to a new wave of excitation before the previous wave of excitation has ended.

The observations of Moe, Harris, and Wiggers (1942) indicate clearly that a suitable electrical stimulus applied to a ventricle during or just before the descent of the T wave leads to a wave of excitation in the heart muscle, but after such a delay that the resulting R wave came after the termination of the T wave and commonly in the vicinity of the U wave. In the course of some observations with Mr. Fastier, direct leads from the surface of the heart have been taken in the dog in the course of the experimental production of ventricular flutter by the administration of amarin followed by adrenaline. In the stage preceding the onset of ventricular flutter we have observed interruption of the terminal deflection of these (direct lead) electrograms (Fig. 10)

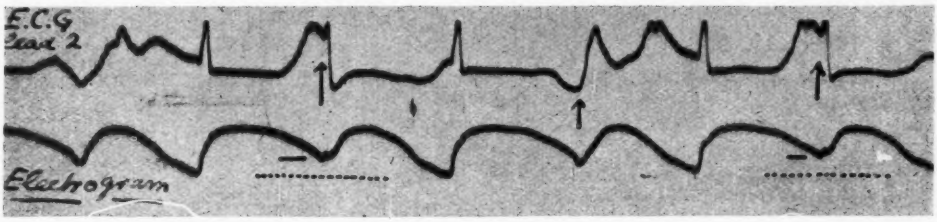


FIG. 10.—Dog (17 kg. 6·3 g.), under sodium barbitone. Vagi intact. The upper trace is an electrocardiogram which shows R waves appearing on T waves just before the onset of ventricular flutter, which was induced with adrenaline (25 μg.) following treatment with amarin.

The lower trace is a simultaneously recorded electrogram, picked up from an electrode that was close to the A-V septum on the left side of the heart. This suggests practically continuous electrical activity in the ventricle at the stage of chaotic rhythm. Note that the electrogram does not always settle down to a base line; where the T wave of the electrocardiogram has been interrupted by the succeeding R wave, the new electrogram may begin prematurely, as judged by the fact that the preceding complex does not fall to the level noted with the alternate series of complexes.

by the succeeding wave of excitation, an observation that corresponds with the appearance of R waves on T waves but suggests that the phenomenon can take place even within the circumscribed area of the heart from which the electrogram is recorded. It is not unlikely therefore, that cardiac muscle fibres are capable, under certain circumstances, of responding to a new wave of excitation before the previous wave of excitation has ended.

Excitability of the Myocardium as the Underlying Cause

The data concerning the 17 patients whose cases are reported suggest the probability that "increased excitability" of the myocardium may be an important underlying cause for the appearance of R waves superimposed upon T waves. It is necessary to consider further the meanings of the word excitability as applied to cardiac muscle. Increased excitability has been used in reference to an increased disposition of the cardiac muscle to originate new rhythms. More precisely, however, it should refer to the ease with which the myocardium responds when a stimulus is applied to it. No doubt, under clinical conditions, these two phenomena are difficult to differentiate from each other but evidence suggesting excitability in one sense or another is present in the great majority of cases here quoted. In Cases 1, 2,

* An additional 8 cases, including one with paroxysms of ventricular flutter (electrocardiographic), have been encountered while this paper was in press.

TABLE I

Case	Age	Type of Interruption †				Polymorphic Ectopic Vent. Complexes	Variability of Interval after antecedent beat	Ectopic Vent. Complexes in runs of 2 or more	Variability of Interval between successive beats	Polymorphic Ventricular Complexes of Supraventric. Origin	Types of Rhythm Encountered	Other Electrocardiographic Evidence of Myocardial Damage	Clinical Features	Progress of Patient	Long or short Lengths of Tracing Available
		S by S	S by V	V by S	V by V										
		Cardiac Infarction Cases													
1	59		?+		+	+	+	+	+	0	Sinus prem. v. s.	T I isoelectric T II low or inverted	*Recent infarction*, congestive failure large heart	D.S.	L.
2	46				+	+	+	+	+	0	Sinus prem. v. s. v. par. tachy.	Intermittent B.B. Bl. Indefinite	*Recent infarction*, good clin. evidence of infarction	R.	S.
6	58		+			+	+	0	n.a.	0	Sinus prem. v.s.	Positive	*Recent infarction*, good clin. evidence of infarction	R.	L.
9	73		+			0	+	0	n.a.	0	Sinus prem. v.s.	Low T I: Positive	*Recent infarction* confirmed P.M.	D.S.	S.
10	77		+			n.a.	n.a.	0	n.a.	0	Sinus prem. v.s.	T I, T IV inverted Q I deep	*Old infarction*, angina of effort	D.	S.
11	79		+			+	+	+	n.a.	0	Sinus prem. v.s.	Positive	*Recent infarction*	D.	S.
		" Myocardial Degeneration " Cases													
5	71		+		+	+	+	+	+	0	Sinus aur. bigem. prem. v.s.	Low T I	*Myocard. degen.*	D.S.	L.
7	40		+		+	+	+	+	+	0	Sinus prem. v.s.	Inverted T III	*Myocard. degen.*, gallop rhythm, œdema ankles	R.	L.
8	77		?+		+	+	+	+	+	+	Sinus prem. v.s.	Isoelectric T I	*Myocard. degen.*, art. hypertension, card. asthma	R.	L.
12	77		+			+	+	+	n.a.	0	Sinus prem. v.s. prem. a.s.	T III isoelectric	*Myocard. degen.*, gallop rhythm	R.	L.
17	62		+			+	+	0	n.a.	0	Sinus prem. v.s.	None	Melancholia, circulatory condition discovered incidentally	R.	L.
		Auricular Fibrillation Cases													
3	56	+	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	+	Sinus par. aur. fibrillation	T I, T II low biphasic Aur. fibrillation	*Thyro-cardiac* improved by thyroidectomy	R.	S.
4	71	+	+	+	+	+	+	+	+	+	Aur. fibr. prem. v.s.	T III low	Confused mental state. Improved in hospital	R.	L.

TABLE I—(*continued*)

TABLE I—(*continued*)

13	78	+	n.a.	n.a.	n.a.	n.a.	n.a.	na.	+	Sinus par. aur. fibrillation heart block	Aur. fibrillation	Large heart Hypostatic pneumonia	D.	S.
14	70	+	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	+	Aur. fibrillation	Aur. fibrillation, T I, II, 1:1 almost isoelectric	Gallop rhythm, Large heart, Great obesity	R.	S.
15	73	?+	?+		+	?	n.a.	n.a.	+	Aur. fibrillation b.b. block	Low T I, B.B. Bl.	*Congestive failure.* Emotional shock	R.	S.
16	66	+	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	+	Par. aur. fibrillation	Abnormally large P wave	Tachycardia, otherwise reasonably fit	R.	L.

† S by S—examples of ventricular complexes of supraventricular origin interrupted by other ventricular complexes of supraventricular origin.
S by V—examples of ventricular complexes of supraventricular origin interrupted by ectopic ventricular complexes.
V by S—examples of ectopic ventricular complexes interrupted by ventricular complexes of supraventricular origin.
V by V—examples of ectopic ventricular complexes interrupted by other ectopic ventricular complexes.
n.a.—not applicable. D.S.—died suddenly. D.—died. R.—recovered.

4, 5, 7, 8, 9, 12, and 17, it seems probable there is an increased tendency to originate new rhythms. Large numbers of premature ventricular systoles arise which, as judged from the shape of the complexes, originate from different foci. These ectopic beats occur at a variable time after the preceding beat and it may be thought from this that they probably result from the spontaneous activity of small parts of the cardiac muscle rather than from excitation of the ventricular muscle as the result of "re-entry" of impulses set up during the antecedent systole.

In contrast to this we have Cases 3, 13, 14, and 16, with auricular fibrillation and an abnormally rapid beating of the ventricles. It may well be thought that the conducting tissue (less probably, ventricular muscle) is responding more readily than usual to the stimuli coming down to it from the auricles.

Of the 17 cases, 6 are examples of cardiac infarction. In such cases the important pathological change in the myocardium is of comparatively recent origin. It is not surprising that in most cases where premature ventricular systoles are the result of a cardiac infarction the ectopic beats appears to arise from many foci. Likewise if these premature beats are arising spontaneously as the result of discharge from irritable foci, there is no obvious reason why they should develop at a fixed time after the antecedent normal complex and in fact, in none of the infarction cases here quoted, do we find the premature ventricular systoles at a fixed distance after the antecedent normal beat.

In the 6 cases of cardiac infarction described in this paper, R waves are found superimposed on T waves, but in most cases of infarction this phenomenon is not found.

R waves superimposed on T waves were found in a miscellaneous group of cardiac cases where there was no cardiac infarction. In some of these patients ectopic beats arising in the ventricles are responsible for most of the interrupted complexes. These premature ventricular complexes arise from several foci and at variable times after the antecedent complexes. It seems probable that there is increased excitability of the ventricular muscle due in these cases to causes other than cardiac infarction. In other cases, however, the rhythm has a supraventricular origin. In most of such cases the evidence of excitability is two-fold, first the development of an irregular auricular tachycardia due in the present cases to auricular fibrillation and secondly the fact that the ventricles are able to respond to these stimuli by unusually rapid beating.

In some patients ectopic rhythms have arisen at one time from the auricles and at another from the ventricles. This observation also favours the idea

that the common factor is an increase in myocardial excitability (Cases 4, 5, 12, and 15). Some further evidence is given in the succeeding section.

The Supernormal Period of Cardiac Excitability

As has been recognized for some time, there is a supernormal period in nerve at the time of the negative after-potential. Adrian (1921) showed that a super-normal period could be demonstrated in the ventricle of the frog upon acidifying the fluid in which the tissue was immersed. Wastl (1922) demonstrated supernormality in fatigued preparations. Cats anæsthetized with barbiturates invariably showed the supernormal period subsequent to the relative refractory period (Hoff and Nahum, 1938) but decerebrated cats rarely showed such super-normality (Eccles and Hoff, 1934). The super-normal period in the cat's ventricle may coincide with the terminal part of the T wave and when a U wave is present it falls during this stage. Wastl (1922) considers that the U wave is in fact the terminal part of the ventricular complex.

It is interesting to consider whether any of the examples of R waves upon T waves are distributed in such a manner that the interrupting beats fall chiefly within a phase of super-normality. Super-normality might be concerned also in the frequency with which the ventricle is stimulated from auricles in a state of auricular fibrillation. If such were the case we would be dealing, presumably, with a super-normality of the conducting tissue. Super-normality of the conducting tissue has been postulated by Lewis and Master (1924) and by Goldenberg and Rothberger (1936). Super-normality might be exhibited in relation to premature ventricular systoles and might determine whether a stimulus arising from an irritable focus would be effective and lead to a premature ventricular complex during the supernormal phase of the antecedent heart beat.

In the cases described in this paper, most premature beats develop either in the U wave region or on the descent of the T wave. In some cases all the premature systoles are confined to these parts of the cardiac cycle. An example of this is found in Case 7. At times when this patient was not displaying R waves on T waves the premature beats occurred a little later in the cardiac cycle and mostly in the region of the U wave. In some other patients (Case 8) the premature beats could occur during a greater part of the cardiac cycle but were concentrated particularly in the region of the U wave or on the descent of the T wave. Similarly, when premature beats interrupted other premature beats or were followed by other premature beats, the R wave of the second beat occurred very soon after the end of the T wave or during its descent. The incidence of the premature beats in these patients could be explained as being largely determined by a super-normal period both in the case of premature beats following normal beats and in premature beats following other premature beats. In most patients where interruptions of premature beats by premature beats is observed, examples of the interruptions of normal beats by premature beats are also observed. The interruption is not so much determined by the nature of the complexes concerned as by a state of the cardiac muscle. Probably, the state of the cardiac muscle that allows the effective generation of these very premature ectopic beats is a state of super-normal excitability of the myocardium. It has been stated by Katz (1946) that a super-normal phase does not occur in the normal human heart but may be present in abnormal hearts. Scherf and Scholt (1939) also describe a super-normal phase in man. The observations reported in this paper are consistent with this view. The super-normal phase has been demonstrated in experiments on healthy cats but it has not yet been made clear whether under experimental conditions the heart was exhibiting a phenomenon that would not be obtained under more normal conditions.

Relationships of Electrical and Mechanical Events when T Waves are Interrupted by R Waves

It is not certain that the relationship between electrical and mechanical events in the heart is constant (Katz, 1946) and it may be changed both during health and in disease. In a number of our cases in which R waves were encountered on T waves phonocardiograms or alternatively ballistocardiograms were recorded simultaneously with the electrocardiograms. In Cases 5 (Fig. 5A, B) and 7 it was found that, where the T wave was interrupted by the R wave of the premature systole, the intensity of the first sound produced by the very premature systole was less than that produced by normal heart contractions or by premature contractions that occur later in the cardiac cycle. Sometimes the weak first sound was followed by a second sound, in other cases no recorded second sound was observed. In those cases where a second sound was associated with a very early premature systole it is realized, with some surprise, that the premature beat must have caused a discharge of blood from the heart and the opening of the semilunar valves must have been sufficient to produce a second sound on closing again. Either the antecedent beat had not emptied the ventricles completely or some degree

of filling of the ventricles must have taken place at a time corresponding to the lower third of the descent of the T wave. Other phonocardiograms gave results that were not dissimilar. In Case 5 several ballistocardiograms were taken (Fig. 5) and these showed, as expected, that the output from the heart was much less when a premature systole occurred very early in the cardiac cycle, but in all traces taken the ballistocardiographic results suggested that some blood had been discharged into the aorta even during the very premature systoles.

The Clinical Significance of R Waves on T Waves and Indications for Treatment

A survey of published electrocardiograms shows that R waves on T waves are often seen shortly before the onset of clinical ventricular flutter, also before the onset of experimental ventricular flutter produced in a variety of ways, and in this series R waves on T waves occurred in 6 patients with cardiac infarction of whom 2 died suddenly. These points indicate the possibility that the appearance of R waves on T waves may be of bad prognostic import. It would appear that the condition occurs chiefly among cases where there is good evidence of increased cardiac excitability and of substantial myocardial damage. Many of the patients were elderly. Naturally enough where there is already evidence of myocardial disease one may expect a poor prognosis; the question we must ask is whether the finding of an R wave on a T wave, in itself worsens the prognosis in these cases. On this question there is insufficient evidence but nevertheless the distinct indication that the subject deserves further study, first because of the known association, under experimental conditions, between the presence of R waves on T waves and ventricular flutter and fibrillation, secondly because in the clinical material studied there had been instances of sudden death that could be explained reasonably as examples of ventricular flutter or fibrillation. The matter is not without practical importance since preliminary observations suggest that the tendency to this particular manifestation can be arrested or greatly diminished by treatment with quinidine, digitalis, or strophanthus, more especially quinidine.

Unfortunately the possibility of a useful method of treatment did not emerge at the outset of this investigation, but in two cases of cardiac infarction exhibiting the presence of R waves on T waves the administration of quinidine arrested the premature systoles, and as premature ventricular systoles had been responsible for the interruptions of the antecedent complexes, this phenomenon was thereby eliminated. In the first (Case 6) the patient made an uninterrupted recovery from the infarction but was readmitted some 3 months later with a second and fatal infarction. On this second occasion there were no premature systoles noted. In the second (Case 9) the administration of quinidine prevented the premature systoles and eliminated the interruption of complexes. Unfortunately a hæmatemesis necessitated withdrawal of the quinidine whereupon the premature ventricular complexes recurred. One month after the onset of the infarction the patient was saying how well he felt and he suddenly stopped and was dead in a few seconds. This would appear to be an example of ventricular flutter. In Case 7 the patient was in moderately good condition with little breathlessness and a moderate exercise tolerance, but a gallop rhythm. She was treated with quinidine; this stopped almost all ectopic beats, but unfortunately the drug had to be stopped as she experienced continuous vertigo and headache. On administering strophanthin by intravenous injection the number of premature systoles were much reduced, and those which occurred were found later in the cardiac cycle and after the termination of the T wave. With eight tablets daily of 1/500 grain of strophanthin by mouth; also, the premature systoles were much reduced in number. In view of the increased excitability of the ventricle brought about by substances such as digitalis and strophanthus, 1/200 of a grain of atropine was given thrice daily at the start; this to some extent at least, serves as an anti-fibrillating agent. The patient was much improved and was discharged from hospital.

It would seem that the administration of quinidine, digitalis and strophanthin in such cases deserves a trial. Perhaps quinidine is the most likely to prove satisfactory and digitalis and strophanthus are probably potentially dangerous. In any case where cardiac infarction has taken place neither digitalis nor strophanthus should be given unless there is congestive heart failure.

Summary

Seventeen cases are described in which R waves appear on the descent of T waves. They appear to be examples of an electrocardiographic syndrome characterized by a group of related abnormalities some of which are explicable in terms of increased myocardial excitability.

The presence of an R wave on a T wave indicates that a new wave of excitation starts before the previous wave has ended. It is convenient in these circumstances to speak of a ventricular complex being interrupted before its completion.

Ventricular complexes of supraventricular origin may be interrupted by other ventricular complexes

of supraventricular origin or by ectopic ventricular complexes. Ectopic ventricular complexes may be interrupted by ventricular complexes of supraventricular origin or by other ectopic ventricular complexes.

R waves on T waves may occur with ectopic ventricular systoles, paroxysmal ventricular tachycardia, auricular fibrillation, and auricular paroxysmal tachycardia. They may occur in cardiac infarction. Theoretically they might occur with ectopic auricular systoles and auricular flutter.

When R waves on T waves are due to ectopic ventricular complexes, these are almost always polymorphic and presumably multifocal. The ectopic ventricular complexes occur at varying intervals after the antecedent beat and there is a tendency for them to occur in runs of two or three or more beats. Even when the presence of R waves is brought about by a supraventricular rhythm (usually auricular fibrillation), polymorphic ventricular complexes are often found.

In view of the fact that R waves on T waves are frequent precursors of clinical and experimental ventricular flutter and ventricular fibrillation, it is desirable to consider the significance of this finding for prognosis in man. A few of the patients in this series have died suddenly.

It is probably advantageous to use quinidine in such patients with multiple premature ventricular systoles. This abolished the interruption of T waves by R waves in all of five cases. Digitalis and strophanthus also abolish the interruptions in some cases, but have theoretical objections.

The significance of this phenomenon in relation to the refractory period of heart muscle, the supernormal phase of cardiac excitability, and the mechanical changes associated with very premature systoles are discussed.

I am indebted to Dr. Laurence Malcolm for permission to use his ballistocardiograph, to Dr. Iverach, Dr. Kirk, and Dr. Harold Palmer for permission to examine cases under their care, and to the New Zealand Medical Research Council for the expenses of the research.

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LAY CARDIOLOGISTS

BY

TERENCE EAST

"For so to interpose a little ease" is well enough in these times, even in a scientific journal. It is hardly fair to complete the quotation, for the "surmise" of the lay writer is often far from "false."* From time to time, in desultory reading, one's attention is arrested by a good description by a lay author of a clinical condition; those which follow are of cardiovascular interest. The description by W. N. P. Barbellion of his disseminated sclerosis in the *Journal of a Disappointed Man* once attracted much interest. He also gave an account of his extrasystoles.

"Bad heart attack all day. Intermittency is very refined torture to one who wants to live very badly. Your pump goes 'dot and carry one,' or say, 'misses a stitch,' what time you breathe deep, begin to shake your friend's hand, and make a farewell speech. Then it goes on again and you order another pint of beer. It is a fractious animal within the cage of my thorax, and I never know when it is going to escape and make off with my precious life between its teeth."

The alarm that these harmless disturbances occasion was also well described by Hugh Walpole in his novel *The Old Ladies*.

"A new sound that May had never heard in that house before. It was the dripping of a tap . . . like someone counting time—1, 2, 3, 4, then a pause; then several drips together. . . . May began to count—she counted to ten and after that so many came together that she could count no longer . . . she lay, the sweat on her forehead, her body trembling, her heart running and jumping and missing, and jumping and running. She heard it so plainly that it seemed that it must be with her now beside her bed, the running tap."

There are many good clinical references in Kipling's writings. The only one of cardiovascular interest is the description in *The Light that Failed* of what would appear to be a patient with aortic regurgitation who has just climbed a flight of stairs, "His lips were parted and pale, and there were deep pouches under the eyes. 'Weak heart,' said Dick to himself as he shook hands, 'very weak heart. His pulse is shaking his fingers.'"

Samuel Johnson diagnosed the cardiac origin of his asthma correctly. Writing to Dr. Brocklesby, his physician, after a visit to Lichfield, he remarked, "The asthma has no abatement. Opiates stop the fit, so that I can sit and sometimes be easy, but they do not procure me the power of motion. I am looking into Floyer, who lived with his asthma to almost his ninetieth year. His book by want of order is obscure; and his asthma not of the same kind with mine." Later in the year he died of heart failure, and the autopsy showed that he had had high blood pressure. His well-known account of his stroke which he had had the year before agrees with this.

"I went to bed, and in a short time waked and sat up, as has long been my custom, when I felt a confusion and indistinctness in my head, which lasted, I suppose, about half a minute. I was alarmed, and prayed God, that however he might afflict my body, he would spare my understanding. . . . I had no pain, and so little dejection in this dreadful state, that I wondered at my own apathy, and considered that perhaps death itself, when it should come, would excite less horror than seems now to attend it.

"In order to rouse the vocal organs, I took two drams. Wine has been celebrated for the production of eloquence. I put myself into violent motion, and I think repeated it; but all was in vain. I then went to bed, and strange as it may seem, I think slept. When I saw light, it was time to contrive what I should do. Though God stopped my speech, he left me my hand; I enjoyed a mercy which was not granted to my dear friend Lawrence, who now perhaps overlooks me as I am writing, and rejoices that I have what he wanted. My first note was necessarily to my servant, who came in talking, and could not immediately comprehend why he should read what I put into his hands.

"I then wrote a card to Mr. Allen, that I might have a discreet friend at hand, to act as occasion

* "For so to interpose a little ease let our frail hearts dally with false surmise."—Milton's *Lycidas*.

should require. In penning this note, I had some difficulty; my hand, I knew not how or why, made wrong letters. I then wrote to Dr. Taylor to come to me, and bring Dr. Heberden: and I sent to Dr. Brocklesby, who is my neighbour. My physicians are very friendly, and give me great hopes; but you may imagine my situation. I have so far recovered my vocal powers, as to repeat the Lord's Prayer with no very imperfect articulation."

He made rapid recovery, and had " leave to wash the cantharides " from his head a fortnight after the stroke, which was no doubt hypertensive encephalopathy.

In *Treasure Island* there is a short vivid description of an apoplectic attack. " I heard a loud fall in the parlour, and running in, beheld the Captain lying full length on the floor. He was breathing very loud and hard; but his eyes were closed, and his face a horrible colour."

Whether the philosopher Seneca * really had angina pectoris is doubtful. He described an attack in these words (*Epistulæ Morales LIX*): " But I have been assigned, so to speak, to one special ailment. The attack is of very brief duration, like that of a squall at sea; it usually ends within an hour. I have passed through all the ills and dangers of the flesh; but nothing seems to me more troublesome than this. And naturally so; for anything else may be called illness, but this is a sort of continued ' last gasp.' Hence physicians call it ' practising how to die.' " As he lived long after and died by his own hand ultimately, perhaps his " meditatio mortis " was really bronchial asthma. In the *Swan of Litchfield* by J. E. Pearson, there is an excellent account of angina of effort, which culminated in a fatal attack on stooping. Anne Seward, the heroine of the book, describes the death of her old friend Mr. Saville, which took place on August 16, 1803.

" In April he began to complain, at times, of a stricture in his breast—a slight pain there, and a difficulty in breathing on going upstairs, or uphill. A disorder so entirely new to his frame startled me, but neither of us supposed the symptoms dangerous. His appetite, his spirits good, and the malady apparently trivial and infrequent; yet alas! I am now convinced these were the presage of the disease which destroyed him." He had been dressing for a party. " Soon after he cut a corn, which pained him, and in that operation had been stooping over his stomach some time, when suddenly a tremendous seizure of the late kind attacked him, and in a quarter of an hour struck him from the land of the living."

* Translation by R. M. Gunmere (Loeb series).

The following passage from *Middlemarch* describes what might well have been a painless attack of myocardial infarction.

" Dorothea had not looked away from her own table when she heard the loud bang of a book on the floor, and turning quickly saw Mr. Casaubon on the library steps clinging forward as if he were in some bodily distress. She started up and bounded towards him in an instant; he was evidently in great straits for breath. Jumping on a stool she got close to his elbow and said with her whole soul melted into tender alarm:—' Can you lean on me, dear? ' He was still for two or three minutes which seemed endless to her—unable to speak or move, gasping for breath. When he at last descended the three steps and fell backwards into the large chair, he no longer gasped, but seemed helpless and about to faint."

His physician, Mr. Lydgate, makes his diagnosis and prognosis. " My conclusions are doubly uncertain, uncertain not only because of my fallibility, but because diseases of the heart are eminently difficult to found predictions on. I believe you are suffering from what is called fatty degeneration of the heart which was first divined and explored by Lænnec. It is my duty to tell you that death from this disease is often sudden. At the same time, no such result can be predicted. Your condition may be consistent with a tolerably comfortable life for another fifteen years or even more. "

Mr. Casaubon was found dead sitting in his summer house, not long after this. The prognosis which George Eliot puts into the mouth of the doctor is cleverly worded, and would be a model of instruction for a student.

An atypical attack of coronary occlusion seems to be the subject of one of Cowper's letters (May 1785).

" Mr. Ashburner, the elder, went to London on Tuesday sennight in perfect health and in high spirits, so as to be remarkably cheerful, and was brought home in a hearse the Friday following. Soon after his arrival in town, he complained of an acute pain in his elbow, another in his shoulder, then in both shoulders; was blooded; took his doses of such medicine as an apothecary thought might do him good, and died on Thursday morning at ten o'clock. It is not common, however, for men at the age of thirty-six to die so suddenly," he comments; in those days, too, early cases appear to have occurred, one may remark.

In Horace Walpole's letters there are many medical references, chiefly on the subject of gout. There is one which may be included here. In one he laments the death of his friend Mr. Chute, also a victim of gout, in a letter to Sir Horace Mann in Florence.

" I was never alarmed till last summer when he had a low lingering fever and sickness, and pain in his breast with returns of the recurrent palpitation. . . . On Thursday last, . . . I was told he was very ill, I found him in bed; he had so violent pain in his breast that two days before he had sent for Dr. Thomas, who had given him one hundred drops of laudanum and asafœtida: Mr. Chute said 'It is not gout, I have had my palpitation and fear it is something of a polypus!' "

He died suddenly. Walpole comments " It certainly was a polypus; his side grew immediately as black as ink." If this account is correct it might possibly have been a dissecting aneurysm, with rupture into the pleura.

To turn to more modern writers, there is a first-rate account of the symptoms of cardiac infarction in *Time Must Stop* by Aldous Huxley.

" And then suddenly the pain was like a red hot poker thro' his chest. . . . He felt dizzy and a whirling blackness obscured the outside world. . . . He lowered himself unsteadily onto the seat and almost immediately felt a good deal better. . . . Just as his arm was at full stretch the pain returned—but in a new form: for now it had become, in some indescribable way, obscene as well as agonizing. And all at once he found himself panting for breath, and in the clutch of a new terror more intense than any he had ever experienced before. Then all at once the pain shot down his left arm, nauseating, disgusting, like being hit in the wind."

Sparkenbroke by Charles Morgan provides another good description of an attack of angina brought on by cold.

" In the evening, a little before dusk, while he was washing in cold water, he received warning that a paroxysm was about to seize him. A stiffness of neck and shoulder was followed by a deep aching within the left arm, and, after a little interval, by an agony within the leg as though a wedge were being driven into the bone's marrow and the bone itself split. He had dragged himself from the washstand to his bed and covered himself, for he was half naked, his body still wet and now bitterly cold. As the pain increased, the leg stiffened; his back arched; his arm, beyond his will, was twisted under his back, and he cried out, for his ampoules of amyl nitrite were in the coat he had taken off. Bissett, hastening in, put one of these into a handkerchief and the handkerchief within the grip of his hand. He crushed it and inhaled. For a little while it gave relief. His body was loosened from its contortion and he lay against pillows, struggling for breath, asking that he might escape the greater paroxysm of the body itself.

" But the agony swept upon him afresh. There appeared in his mind an image of his chest as a bony shell within which the organs of his body were being compressed by cords. The organs themselves had individuality and voices; he heard them cry out, saw them twist and spurt, emptying their blood-red to a pearly and sweating grey. Far off, within the divisions of his fingers, were folds of linen; he raised them up; a handkerchief was twined against his nostrils, which sucked in its fumes. They had the smell of comfort, but a gust of torment swept them away, and he saw Bissett laying hot compresses on the bony shell, which heat could not penetrate. . . . He gathered his knuckles into the softness of his throat." *

The art of writing clinical descriptions is almost lost nowadays. The dry deserts of modern medical literature would make better reading if something of the charm of these lay authors could be imparted to them!

* Some of these excerpts, with others less pertinent to cardiology have appeared in the *King's College Hospital Gazette* (1947), Vol. 26.

EDITORIAL NOTE

What was almost certainly a paroxysm of auricular fibrillation has been described in the literature of the 1914–18 war, when the author was almost exhausted by the hardships involved in escaping on foot from a prisoner's camp: " Owing to the mud I began to feel frightfully tired. I staggered, and quite suddenly I collapsed and lay on the ground unable to move. I managed to put my hand over my heart and could feel that it was running most irregularly and misfiring in an extraordinary way. After about a quarter of an hour it got much better, so I had a few mouthfuls of bread and went on again." (*The Escaping Club*, by A. J. Evans. John Lane, Lond., 1929, p. 224). The sudden collapse and the sudden recovery make it much more likely that this was paroxysmal fibrillation than a bout of frequent extrasystoles.

East has included cardiovascular disease and this allows a reference to the cardiovascular accidents that give more play to the lay writer because their results are more obvious in disorders of behaviour and mannerisms. Charles Dickens has many such

instances and shows by these, as in other ways, his great powers of accurate observation. The mental changes and change of temperament in Mrs. Gargery in *Great Expectations* after a blow on the back of the head, and the detailed account of the degenerative changes following on cerebral arteriosclerosis on the Honourable Mrs. Skewton, the mother of *Mrs. Dombey*, are detailed and accurate and must have been based on personal observation of cases. These have been dealt with fully by Russell Brain in the *London Hospital Gazette*, January 1942. He is able to diagnose that Mrs. Gargery had a severe contusion of the left temporoparietal region causing jargon aphasia and word deafness and some traumatic dementia, with injury to the third or sixth cranial nerve leading to diplopia.

An equally detailed diagnosis of a hæmorrhage from a posterior inferior cerebellar artery in the case of James Armitage, alias Trevor (*The Gloria Scott*) could be made from the pages of *Conan Doyle*, but perhaps this is an unfair addition as medical authors have been excluded. Even so, readers who look for it may be surprised by the amount of accurate medical detail in the Sherlock Holmes stories. Major Sholto died from left ventricular failure, and orthopnœa is rightly emphasized as a leading symptom. "When we entered his room he was propped up with pillows and breathing heavily . . . grasping our hands he made a remarkable statement in a voice broken as much by emotion as by pain. . . . At this instant a horrible change came over his expression—his eyes stared wildly, his jaw dropped, and he yelled, 'Keep him out.' We rushed to the window and when we returned his head had dropped and his pulse ceased to beat." (*The Sign of Four*). No wonder his son, Thaddeus Sholto, became hypochondriacal about his mitral valve.

The other is a good description of an aortic aneurysm. When Jefferson Hope was arrested he remarked that he might not live for the trial. "It isn't suicide I am thinking of; put your hand on my chest," he said. Watson did so and at once became conscious of an extraordinary throbbing and commotion inside. The walls of his chest seemed to quiver as a frail building would when some powerful engine was at work. In the silence of the room he could hear a dull humming and buzzing noise which proceeded from the same source. Watson diagnosed an aortic aneurysm and the diagnosis was confirmed by his death from its rupture that afternoon (*The Study in Scarlet*).

I have dealt more fully with these medical aspects in the *Guy's Hospital Gazette* (Vol. 48, p. 524, 1934 and Vol. 49, p. 2 and 27, 1935).

MAURICE CAMPBELL.

THE DURATION OF NORMAL HEART SOUNDS

BY

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The gradually increasing importance of phonocardiography creates problems that at times are difficult to solve—among them, that of deciding whether the complexes revealed by a tracing are still within normal limits. Therefore, knowledge of exact normal data is of interest as a basis for the study of clinical tracings.

Many authors studied the normal heart sounds between 1907 and 1937. Their data have been reviewed and can be found in a comprehensive work by Rappaport and Sprague (1942). As, however, those studies were made by means of various techniques, any comparison with our data is impossible and their detailed quotation needless.

The only article that dealt with the same problem and used a similar technique is by Rappaport and Sprague (1942). Our study was made by means of the stethoscopic microphone; therefore, reference will be made only to data obtained by those authors using this microphone.

Rappaport and Sprague studied 33 normal persons between the ages of 19 and 38, and gave the maximal and minimal duration of the heart sounds recorded at the apex (Table I). No average data were given by them.

While these data are extremely useful, they are not sufficient for clinical studies because (*a*) they refer to only one age group, (*b*) they give only the total duration without breaking down the sounds into their various phases, and (*c*) no average figures are given. For these reasons, an additional, more comprehensive study was considered necessary.

The Main Phases of the Cardiac Sounds

As known, the first and second sounds are actually "noises," consisting of various vibrations having different frequencies. Both the first and the second sounds are caused by four different factors. Four different components were, therefore, described in both the first (Orias and Braun Menendez, 1939) and second sounds. (Rappaport and Sprague, 1941 and 1942)

The systematic clinical use of phonocardiography convinced one of us (Luisada) of the extreme variability of the complexes of the heart sounds even in normal subjects. In many of these, separation of the complexes into four components is impossible. On the other hand, the occasional observation of cases where the large vibrations of either the first or the second sound are far more numerous than in the average tracing forces one to know not only the overall duration of the sounds but also the duration of their individual components. For this reason, while we fully recognize the accuracy

TABLE I

Data of Rappaport and Sprague

	First sound (sec.)	Second sound (sec.)	Third sound (sec.)	Interval II–III (sec.)
Maximum duration	0·165	0·145	0·085	0·240
Minimum duration	0·105	0·085	0·030	0·160

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and the theoretical importance of dividing the sound complexes into many components, we think that a simplified system of study may have practical value. The following description is based on purely practical considerations.

In both the first and second sounds, the main part of the complex consists of large irregular vibrations, caused in the main by valvular events, while the beginning and the end of the sound is formed by slower vibrations. Therefore, division of each sound into three phases is relatively easy (Fig. 1).

Tables II and III show the causes of these phases and correlate them with the various components of each sound.

As will be noted, our division into components of the first sound is slightly different from that of Orias and Braun Menendez (1939) for the following reasons.

(*a*) The muscular factor gives vibrations that may be superimposed on all the others. On the other hand, a slow vibration frequently initiates the first sound in cases of complete A-V block or auricular fibrillation. This is due to the isometric contraction of the ventricles. It is difficult to say whether the heart muscle itself is causing it or whether it is due to initial vibrations of the mitral and tricuspid valves preceding their closure.

(*b*) The valvular factor gives vibrations that

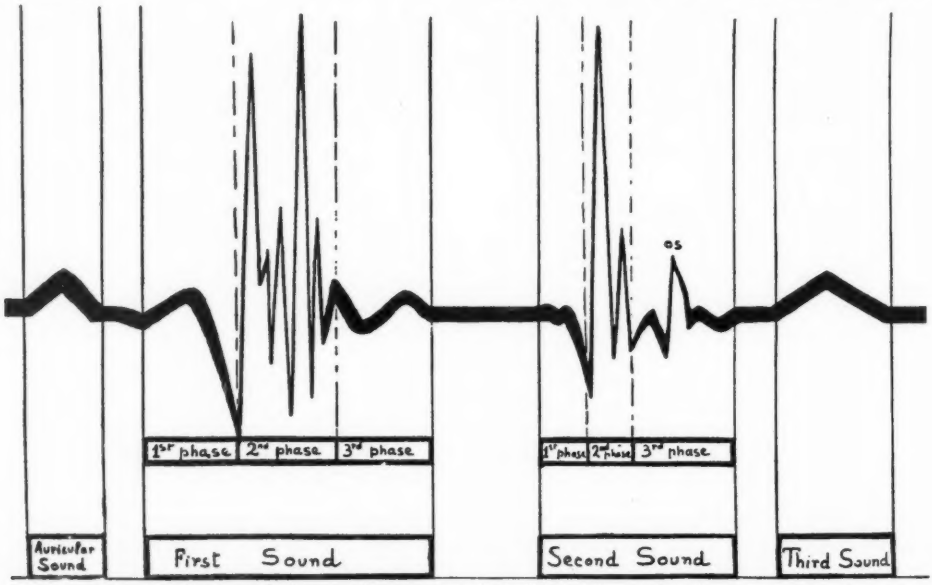

FIG. 1.—Diagram of a normal phonocardiogram recorded with a stethoscopic microphone. Practical division of the first and second sounds into three main phases.

TABLE II

CAUSAL AND PRACTICAL DIVISION OF THE FIRST SOUND COMPLEX

Component	Cause	Type of vibration	Phase (new terminology)
1st	Auricular residual vibrations	Coarse Small	1st phase, or phase of the coarse, initial vibrations
2nd	Vibrations due to the isometric contraction of the ventricles	Coarse Small	
3rd	Vibrations due to the closure of the A-V valves	Fine Large	2nd phase, or phase of the fine, large vibrations
4th	Vibrations due to the opening of the semilunar valves.	Fine Large	
5th	Vibrations due to the ejection of blood and to arterial distention	Coarse Small	3rd phase, or phase of the coarse, final vibrations

TABLE III

CAUSAL AND PRACTICAL DIVISION OF THE SECOND SOUND COMPLEX

Component	Cause	Type of vibrations	Phase (new terminology)
1st	Vibrations preceding the closing of the semilunar valves	Coarse Small	1st phase, or phase of the coarse, initial vibrations
2nd	Vibrations caused by the closure of the semilunar valves	Fine Large	2nd phase, or phase of the fine, large vibrations
3rd	Arterial vibrations	Fine or coarse Small	
4th	Vibrations due to the opening of the A-V valves	May be fine Usually coarse and small	3rd phase, or phase of the terminal vibrations

often are clearly separated (Fig. 2 and 3) and may even cause an audible splitting of the sound. Both A-V valve closure and semilunar valve opening are accompanied by rapid large vibrations. The latter are clearly separated from the following vibrations of vascular origin.

On the contrary, the theoretical division of the second sound into four components, as made by Rappaport and Sprague, is exact and should not be changed. It should be pointed out, however, that the vibration due to the opening of the mitral valve may become audible even in normal subjects and give a high wave on the tracings, as reported by one of us (Luisada, 1943 and 1948) and shown by Fig. 4.

RESULTS OF THE STUDY

Our study was based on the private collection of one of us (Luisada), consisting of over 1500 phonocardiograms. Cases with a clinical diagnosis of heart disease, an abnormal electrocardiogram, or a recorded murmur were excluded. This left 185 cases which, grouped by age, were divided as follows:

(*a*) 4 cases of fœtal sounds recorded during various stages of pregnancy.
(*b*) 1 case below 4 years of age.
(*c*) 2 cases between 4 and 10 years of age.
(*d*) 7 cases between 11 and 20 years of age.
(*e*) 56 cases between 21 and 40 years of age.
(*f*) 38 cases between 41 and 60 years of age.
(*g*) 17 cases above 60 years of age.

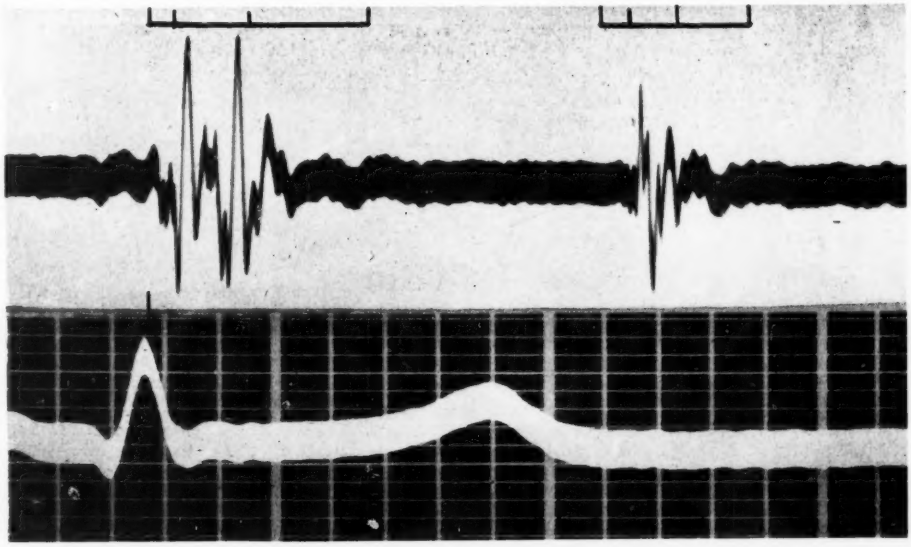

FIG. 2.—Phonocardiogram of a normal subject, aged 24 years. The first sound presents two higher vibrations in phase 2.

On account of the small number below 10 years of age, the average figures were made only for those above that age. In each case, the study was made on phonocardiograms recorded by means of a Stetho-cardiette and a stethoscopic microphone with a large funnel *; only tracings recorded at the apex (181 cases) and at the aortic area (73 cases) were considered (fœtal sounds excepted).

The data that were measured were as follows.

(1) Duration of the auricular sound from beginning to end.

(2) Total duration of the first sound, from the beginning of the coarse initial deflection to the end of the last coarse vibration of vascular origin.†

(3) Partial durations of the three phases of the first sound (coarse initial vibrations, high and fine central vibrations, and coarse final vibrations).

(4) Total duration of the second sound, from the beginning of the coarse, initial vibrations to the end of the coarse final vibrations.

(5) Partial duration of the three phases of the second sound (coarse initial vibrations, high and fine central vibrations, and coarse final vibrations including the opening sound of the mitral valve).

(6) Interval between the beginning of the auricular sound and the beginning of the first sound (a–I).

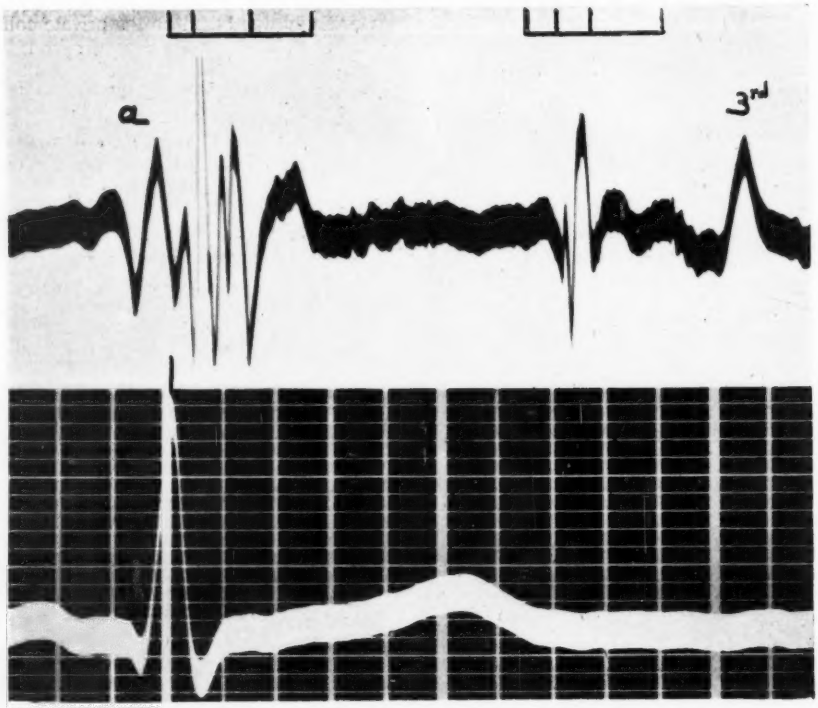

FIG. 3.—Phonocardiogram of a boy of 15 years. Loud auricular sound very close to the first sound; third sound. In this case, an arbitrary setting of the beginning of the first sound at the peak of R wave of the electrocardiogram would have been necessary as no clear-cut division exists between auricular and first sounds.

* In the adults, a funnel having 5 cm. of diameter was used; in children, a smaller funnel having a diameter of 3·7 cm. was preferred.

† In a few cases, it was noted that the auricular sound gave vibrations lasting up to the beginning of the phase of large vibrations of the first sound. In others, no vibration of a coarse type preceded this phase. In order to obtain a clear-cut point in such cases, the peak of the R wave of the electrocardiogram was taken as the initiation of the first sound as an arbitrary and practical reference which may entail a slight error.

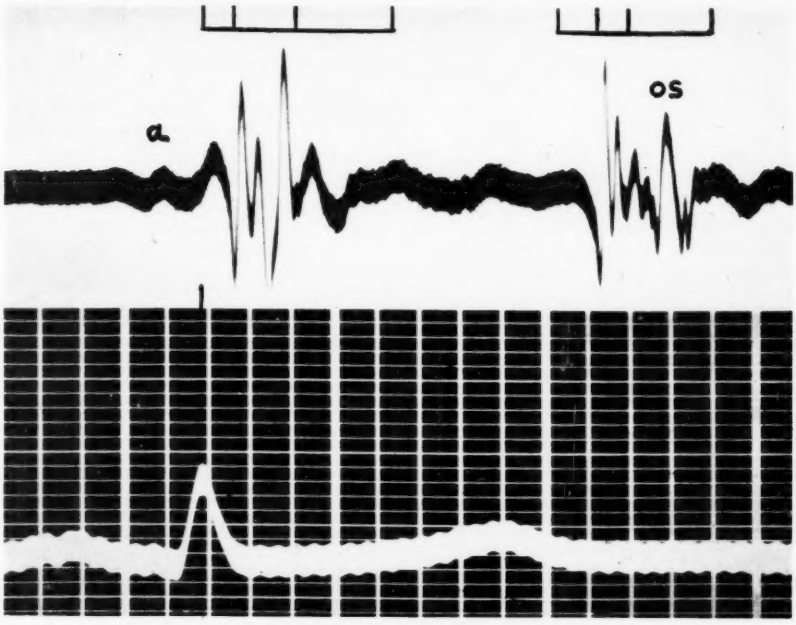

FIG. 4.—Phonocardiogram of a normal woman of 33 years. Two higher vibrations are present in phase 2 of the first sound. The second sound includes a high vibration (os) at the opening of the mitral valve.

The subject has been followed for eight years since this tracing and repeated phonocardiograms recorded. No heart disease was ever recognized. Subsequent tracings indicated a more conventional aspect of the second sound.

(7) Interval between the peak of the largest oscillation of the second sound and the beginning of the third sound (II–III).

The results of the study are reported in the following tables. Occasional small differences occur between the average figure of the total duration of the first or second sound and the average sum of the three phases of each. This is due to the fact that the first phase was measured only in a percentage of cases (indicated in parenthesis) while in others, with no visible vibration occurring in that phase, no measurement was possible.

A summary of the protocols of our observations is given here. Table IV shows the average duration of the heart sounds and their phases and Table V indicates the extreme variations of these sounds.

The average length of the first sound above the age of 10 *was found to be* 0·146 *sec. at the apex and* 0·140 *sec. at the aortic area.*

The average length of the second sound in the same conditions was found to be 0·097 *and* 0·104 *sec., respectively. That of the third sound was found to be* 0·059 *and* 0·042 *sec.*

The average interval separating the beginning of the auricular sound from that of the first sound was found to be 0·058 sec. for both areas; while that separating the main oscillation of the second sound from the beginning of the third, 0·15 sec. at the apex and 0·17 sec. at the aortic area.*

The extreme variations of the first and second sounds are indicated in Table V. Between the ages of 11 and 20, the first sound varied from 0·12 to 0·16 sec. at the apex and from 0·11 to 0·16 at the aortic area; and the second sound, from 0·08 to 0·18 sec. at both areas.

Between the ages of 41 and 60, the first sound varied from 0·07 to 0·22 sec. at the apex and from 0·09 to 0·22 sec. at the aortic area; and the second sound, from 0·05 to 0·16 and from 0·06 to 0·14 sec., respectively.

* The latter figure was obtained on a small percentage of the cases (9 per cent).

TABLE IV

AVERAGE DURATION OF THE HEART SOUNDS, THEIR PHASES AND THEIR INTERVALS *

Age groups (years)	First Sound (sec.)				Second sound (sec.)				III sound (sec.)	a–I (sec.)	II–III (sec.)
	Total	1st phase	2nd phase	3rd phase	Total	1st phase	2nd phase	3rd phase			
Fœtal sounds	0·085	0·010	0·025	0·055	0·055	0·010	0·027	0·020	—	—	—
Below 4	0·070	—	0·040	0·030	0·060	—	0·020	0·040	—	—	—
4–10	0·120	—	0·040	0·080	0·065	—	0·015	0·050	0·050	0·060	0·12
	0·145	0·020	0·070	0·065	0·110	0·010	0·055	0·050	0·040	0·060	0·14
11–20	0·147	0·016	0·069	0·071	0·097	0·018	0·015	0·056	0·050	0·060	0·14
	0·147	0·010	0·064	0·066	0·120	0·020	0·034	0·056	—	0·055	—
21–40	0·146	0·020	0·063	0·078	0·107	0·020	0·028	0·069	0·061	0·064	0·16
	0·145	0·020	0·060	0·071	0·114	0·018	0·043	0·055	0·043	0·072	0·18
41–60	0·149	0·020	0·057	0·080	0·097	0·016	0·024	0·068	0·057	0·061	0·18
	0·144	0·020	0·064	0·068	0·098	0·013	0·040	0·053	0·040	0·052	0·19
Above 60	0·141	0·024	0·050	0·080	0·087	0·020	0·025	0·053	—	0·050	—
	0·123	0·023	0·063	0·054	0·085	0·010	0·038	0·044	—	0·060	—
Overall averages for ages above 10 years	0·146	0·020 (46%)	0·060	0·077	0·097	0·018 (46%)	0·023	0·061	0·059 (50%)	0·058 (78%)	0·15 (50%)
	—		—	—	—		—	—			
	0·140	0·020 (55%)	0·063	0·065	0·104	0·015 (38%)	0·039	0·052	0·042 (9%)	0·058 (45%)	0·17 (9%)
	—		—	—	—		—	—			

* NOTE: The top figures refer to measurements at the apex; the figures below are those from the aortic area.

TABLE V

EXTREME VARIATIONS OF THE HEART SOUNDS AND THEIR MAIN PHASES

Ages	First sound				Second sound			
	Maximum (sec.)		Minimum (sec.)		Maximum (sec.)		Minimum (sec.)	
	Total duration	2nd Phase	Total duration	2nd phase	Total duration	2nd phase	Total duration	2nd phase
APEX								
11–20	0·16	0·12	0·12	0·04	0·12	0 04	0·08	0·01
21–40	0·22	0·10	0·09	0·02	0·18	0·08	0·04	0·01
41–60	0·22	0·10	0·07	0·03	0·16	0·05	0·05	0·01
AORTIC AREA								
11–20	0·16	0·08	0·11	0·06	0·12	0·04	0·08	0·03
21–40	0·22	0·10	0·10	0·03	0·16	0·10	0·08	0·03
41–60	0·20	0·09	0·09	0·04	0·14	0·06	0·06	0·02

At the apex, the maximum duration of the second phase, that of the large oscillations, was found to be 0·12 sec. for the first sound and 0·04 sec. for the second sound in the younger age group; 0·10 and 0·08 sec., respectively, for the group between 21 and 40; and 0·10 and 0·05 sec. for the older age group. At the aortic area, these same oscillations measured 0·08 and 0·04 sec. for the first group; 0·10 sec. for both sounds, for the second age group; and 0·09 and 0·06, for the group between 41 and 60.

On the other hand, the *average duration* of this phase was found to be 0·06 sec. for the first sound and 0·023 sec. for the second, at the apex; and 0·063 and 0·039 sec., respectively, at the aortic area.

Discussion

A comparison of our data with those of Rappaport and Sprague (1941, 1942) shows that our figures were found to be longer for both sounds and also for maxima and minima. This may be explained partly by the larger number of subjects studied and partly by the different way of measuring the sounds which, in our case, is illustrated by Fig. 1.

We believe that breaking the sounds into three phases provides an easier and more rapid method of determining the length of the most important phase, that of large oscillations, which are chiefly connected with valvular events of the heart.*

As a study of the protocols will show, a total duration of the sounds (chiefly of the first sound) that far exceeds the average is found in only a few stray cases. This total duration is increased because the third phase, mainly due to coarse vascular vibrations, is longer than average. This observation increases the importance of separately measuring the three phases of each sound.

* Whenever an accurate break-down of the sounds into their components is necessary because the phonocardiogram is used as a time reference for other tracings (cardiogram, phlebogram, pneumocardiogram, or fluorocardiogram), the division should follow the lines previously indicated by Orias and Braun Menendez and by Rappaport and Sprague with the slight modification indicated in Table II for the first sound complex.

Summary and Conclusions

The authors have studied the duration of the heart sounds and their intervals in a series of phonocardiograms recorded in 185 normal subjects, making use of a stethoscopic microphone.

The difficulty in the measurement of the normal heart sounds led the authors to propose a new practical division of these in the phonocardiogram for general clinical work. Both the first and the second sounds are divided into three phases—the first phase of small and slow vibrations, the second of high and rapid vibrations, and the third of small and slow vibrations.

A sound should be considered abnormal not only when its total duration is prolonged but also when the duration of the phase of large vibrations is beyond the maximum normal duration of that phase.

For each of the various age groups, total duration and partial durations of the sounds were measured by the authors. Maximum and minimum and average figures are given. The intervals between auricular sound and first sound, and those between the second and third sounds are also studied in the various age groups.

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A LOUD-SPEAKER STETHOSCOPE FOR CLINICAL TEACHING

BY

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An equipment was required that would enable a number of students to listen simultaneously in auscultation of a patient's chest. The method adopted is to pick up the sounds by means of a microphone held on the chest, amplify them electrically, and reproduce them at a loud-speaker. The problem differs from that of phonocardiography in two main respects: first, the subjective effect on the listener must be as similar as possible to auscultation with a stethoscope, which means that certain components of the sounds, too small to affect the phonocardiograph record, must be faithfully reproduced, and at the same time frequencies that are not well picked up by a stethoscope must be correspondingly attenuated by the electrical system; and secondly, oscillation (" howling ") is liable to occur due to the microphone picking up the air-borne sound from the loud-speaker.

There is also a fundamental difficulty. The relative sensitivity of the human ear to different frequencies depends on the amplitude of the sound, so that if, by one setting of the amplifier, a student at a certain distance from the loud-speaker hears exactly what he would hear with a particular stethoscope, another at a different distance will not get the same subjective effect. If a high standard of fidelity is demanded, this fact probably limits the method to fairly small groups.

Again, students at a little distance from the patient are at a disadvantage with regard to discrimination, conscious or subconscious, against sounds due to accidental movements of the chest-piece on the skin, and to discrimination against breath sounds when listening to heart sounds and murmurs, because they cannot see small movements. Thus it might be that the best results would be obtained by a compromise that sacrificed fidelity slightly in order to reduce the relative amplitude of such sounds.

Finally there are technical difficulties due to the very low frequencies of the important sounds, which go below the range of all but the best commercial acoustic equipment, and due to the great range of amplitude from the large very low-frequency components of the first heart-sound to the smallest audible murmur.

In the equipment described in this paper, the main difficulties have been overcome, and satisfactory reproduction is believed to have been achieved for at least twenty students at a time. No actual teaching has been done with the equipment at the time of writing. The total cost, apart from time, was about £70.

Discussion of the Problem in the Light of Previous Work

The equipment is required to pick up from the chest normal and pathological cardiac and respiratory sounds, and to reproduce them by a loud-speaker to give as nearly as possible the same effect as auscultation with a stethoscope. Extraneous sounds, such as those due to friction on the skin and air-borne sounds of all kinds, are not required and should be reproduced as little as possible consistent with the main requirement. For the design of the equipment, therefore, information is required on the frequency response of stethoscopes and on the range of frequency covered by the wanted sounds. The equipment should be designed so that the frequency response is the same as that of a stethoscope over this wanted range of frequency, and outside this range the less the response the better.

Cabot and Dodge (1925) studied the frequency distribution of heart and breath sounds, mainly pathological, over the range 30 to 2600 c/s, by a method that is directly applicable to the present problem. They switched different filters in turn into their amplifier and listened for any change in the quality of the sounds as reproduced by it. They

* Vans Dunlop Scholar in Physiology, University of Edinburgh.

found that all components of heart sounds and murmurs were below 1000 c/s, and most were below 600 c/s. The lower limit was in some cases 120 c/s, but in others there were components down to the lower limit of their apparatus. Breath sounds were almost entirely within the range 120 to 1000 c/s. At the date of their work the electrical equipment can hardly have been good enough to give a high standard of fidelity. Brooker (1946), who describes the equipment used in making gramophone recordings for Stokes (1946), found that although most of the energy in the sounds was below 1500 c/s, an amplifier that cut off above 2000 c/s did not give perfect reproduction, and he used one which went up to 4500 c/s in spite of the accompanying disadvantage of increased background noise. The lower limit of his amplifier was 30 c/s, but he believed that lower frequencies were present and influenced the total subjective effect.

Mannheimer (1940) has analysed heart sounds and murmurs in normal children and children with congenital heart disease. He used amplifiers incorporating combinations of good filters with measured characteristics, covering a number of frequency bands, the lowest being 0 to 100 c/s and the highest 500 to 1000 c/s. In different cases he found components both of normal sounds and of murmurs in all his frequency bands. His apparatus (which was primarily for phonocardiography) cut off all components above 1000 c/s, and this he found advantageous in reducing the effect of air-borne disturbances.

The absolute measurement of the frequency response of a stethoscope is difficult. In the conditions in which it is used, the frequency response depends not only on the design of the instrument itself, but also on the degree of acoustic mismatching both where the sound is transferred from the patient's body to the chest-piece and where it is transferred from the ear-pieces to the physician's ears, and unless special precautions are taken the degree of mis-matching at one or both places will be different under the conditions of the experiment from that under practical working conditions. It is of course also necessary to know and correct for the frequency response of the source of sound (e.g. a loud-speaker), and of the microphone and other apparatus used for measuring the amplitude transmitted by the stethoscope. No account has been found of a measurement of this kind in which a full technical description of the apparatus has been given, and it seems likely that authors have failed to realize the importance of reproducing exactly the acoustical mis-match which occurs in practice. A technique in which these matters are fully taken account of, is described in a Medical Research Council Special Report (1947), and was used for measuring the performance of hearing aids. Some such technique could be applied to measurement of the frequency response of a stethoscope, but as far as I know this has not been done.

Rappaport and Sprague (1941) have attempted to measure the frequency response of stethoscopes and give a theoretical response curve for an amplifying stethoscope which should reproduce the effect of " a theoretically average acoustical stethoscope," but it does not seem that their technique was adequate for the reasons just discussed. Their curve falls off steadily from 200 c/s downwards, to −20db at 30 c/s.

Comparison of the effects of different stethoscope chest-pieces is not so difficult. By putting a source of sound in the heart of a cadaver and applying the different chest-pieces to the chest, Johnstone and Kline (1940) closely simulated the conditions of clinical use as far as the acoustical mis-match at that end was concerned. They compared different stethoscopes over the range 20 to 800 c/s, and from their curves it appears that the main effect of a diaphragm, compared with an open bell, is to attenuate the lower frequencies and so increase the relative high-frequency response.

Many whole loud-speaker equipments for teaching are mentioned in papers from 1920 onwards, but usually without precise information about frequency response. Gamble and Replogle (1924) describe the apparatus used by Cabot (1923), and Gamble (1924) describes improvements to the apparatus and the results of experience after a few months' use. Their trials with loud-speaker reproduction were unsatisfactory, and they used a telephone type of output device to which an ordinary stethoscope was applied. They found that a filter cutting off sounds above 660 c/s gave the best results for routine use, and that additional filters were useful for accentuating particular sounds and murmurs, in particular one passing frequencies below 140 c/s and one passing frequencies above 130 c/s. Rappaport and Sprague (1941) discuss the reasons for poor results with loud-speaker equipments, and emphasize the importance of adequate loud-speaker power-handling capacity and freedom from resonances, as well as correct frequency response of the whole equipment. The advantages of loud-speaker reproduction for teaching purposes are discussed by Henriques (1937).

As regards choice of microphone, since the introduction of the piezo-electric crystal microphone this has been unanimously accepted as the best type for the purpose (e.g. by Sacks and Marquis (1935) and Rentschler (1936), etc.). My own experiments with a few other types which happened to be available agree with this.

Characteristics Required for the Equipment

The simplest method of getting a controlled frequency response is to use a microphone and a loud-speaker that both have a response approximately independent of frequency over the range concerned, and to incorporate suitable filters in the amplifier. The range to be covered is from about 30 c/s up to at least 1000 c/s, and probably up to 4000 c/s.

A piezo-electric crystal microphone covers the frequency range satisfactorily; but because of its high impedance it is necessary to keep the capacity of the lead to the first stage of the amplifier low (in the region of 0·0001 microfarad) in order to maintain the response at the upper end of the frequency range. The amplifier input impedance must be high; suitable input circuits are given in *Radio Designer's Handbook*, chapter XI. It is desirable to separate the amplifier from the microphone so that the latter can be mounted in a small light unit, to be placed directly on the chest. High sensitivity to vibrations from the chest-wall, and low sensitivity to air-borne sound and to friction on the case, are required.

The loud-speaker must have a response maintained to the lowest audible frequencies, and portability is an advantage. It must be free from resonances in the lower audio-frequency range, and must also have a power-handling capacity much greater than the mean power to be broadcast, because the very large amplitude low-frequency components in the heart-sounds, which are almost inaudible themselves because of their low frequency, cause chattering or booming in a small loud-speaker.

The amplifier must have a response maintained up to about 4000 c/s, and down to the lowest audible frequencies, though some falling off below 200 c/s is probably required to simulate a stethoscope frequency response. Adjustable filters are required to reduce the low-frequency response and simulate a diaphragm stethoscope, and to reduce the high-frequency response and discriminate against extraneous sounds, which tend to have higher frequencies than the wanted sounds. Further adjustment of the frequency response is desirable so that an attempt may be made to emphasize a particular sound or murmur. The filter and volume controls must be early enough in the amplifier circuit to avoid "limiting" at any stage, but as late as possible, consistent with this, to give quietness in operation. These controls should be within reach of the physician who holds the chest-piece. The distortion-free output of the amplifier need not be as great as the power-handling capacity of the loud-speaker, because the largest amplitudes are at frequencies that are very little heard as sound and do not need to be faithfully reproduced; indeed, a certain degree of relative reduction of the largest amplitudes is probably desirable.

Finally, simplicity of operation is important in an equipment to be used for teaching.

Description of the Apparatus

Apparatus has been assembled that fulfils very nearly the requirements set out in the previous section. The block diagram (Fig. 1) indicates the arrangement of the different units. A small microphone is used like a stethoscope chest-piece, and its output is carried by 6 feet of rubber-protected screened wire to the pre-amplifier. This is housed in a metal box 6 × 6 × 2¼ inches, which also contains the volume control and the tone-control filters. This box lies on the bed or a locker, and the three controls, treble, bass, and volume, are operated by rotating knobs. Thus all the control can be done by the physician who handles the microphone. The output from the pre-amplifier and the power supplies to it are carried by a multi-core cable 11 feet long, connecting it with a larger box 17 × 10 × 9 inches, which contains the main amplifier and all the power supply. (The whole apparatus is supplied from A.C. mains.) The output is led to the loud-speaker by 20 feet of twin flex, with an optional extension of another 35 feet. The loud-speaker cabinet is of wood, and measures 31 × 18 × 18 inches.

Microphone. The microphone at present in use consists of a small piezo-electric crystal unit mounted at the apex of a hollow cone turned out of a cylin-

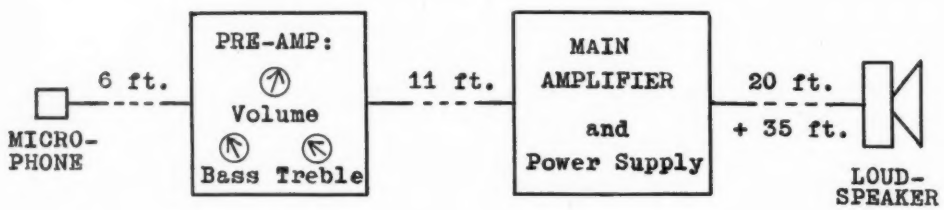

Fig. 1.—Block diagram of the complete loud-speaker stethoscope.

rical block of brass. This is chromium-plated, and is held in the hand in direct contact with the chest. The diameter of the orifice is 1 inch; the total weight is 5 oz. Noises due to friction are no worse than with an ordinary stethoscope. Provided the microphone is in contact with the skin all round its rim, there is little tendency to "howl," and in most cases "howling" is not the factor that limits the maximum useful amplification. The frequency response of this type of microphone (without moving parts other than the crystal itself) can be made practically uniform, but here it is being used with a lower amplifier input impedance than is recommended, which probably reduces the response at the lower frequencies.

It is intended to try other types of crystal microphone, as further improvement may still be possible.

Amplifier. A high-quality audio-frequency amplifier* was modified to suit the special requirements. It consists of two triode stages as pre-amplifier giving a voltage gain × 850, followed by a filter circuit with treble and bass controls and middle-frequency attenuation ÷ 10 (20db), a potentiometer volume control, an amplifier and phase-splitter stage, and a push-pull power output stage. The amplifier gives an output of 12 watts for an input to the first stage of 20 millivolts r.m.s. The input impedance (first grid leak) is 1·5 megohm.

* The amplifier "QA12/P," supplied by The Acoustical Manufacturing Co. Ltd., Huntingdon.

The principal modification required was in the filter circuit, which is shown in its final form in Fig. 2. It is a resistance-capacity network with separate high-frequency and low-frequency controls, which, in the modified circuit, are not entirely independent in their effects. The frequency response curves for the middle and extreme settings of the two controls are shown in Fig. 3 and 4.

The filter controls and the volume control are silent in operation. No trouble was encountered from valve noise or microphony. In the cable connecting the pre-amplifier to the main amplifier there was considerable pick-up of hum from H.T. and L.T. supplies, which was overcome by additional smoothing in the case of the former, but for the L.T. a separate transformer was necessary, as spikes at 200 c/s recurrence were generated in the main transformer and were picked up by the signal lead from the heater leads. With these alterations, the hum from the equipment itself is barely audible, and the measured level in an electrical laboratory was 80 mv. r.m.s. across the 15-ohm output, part of this being due to pick-up from other sources.

Loud-speaker. The loud-speaker is a 15-ohm, 15-watt, 12 inch unit in a special cabinet mounting.* This type of mounting is probably the best to combine robustness and portability with a good low-

* "Labyrinth Loud-speaker, Type SL.15," supplied by The Acoustical Manufacturing Co. Ltd., Huntingdon.

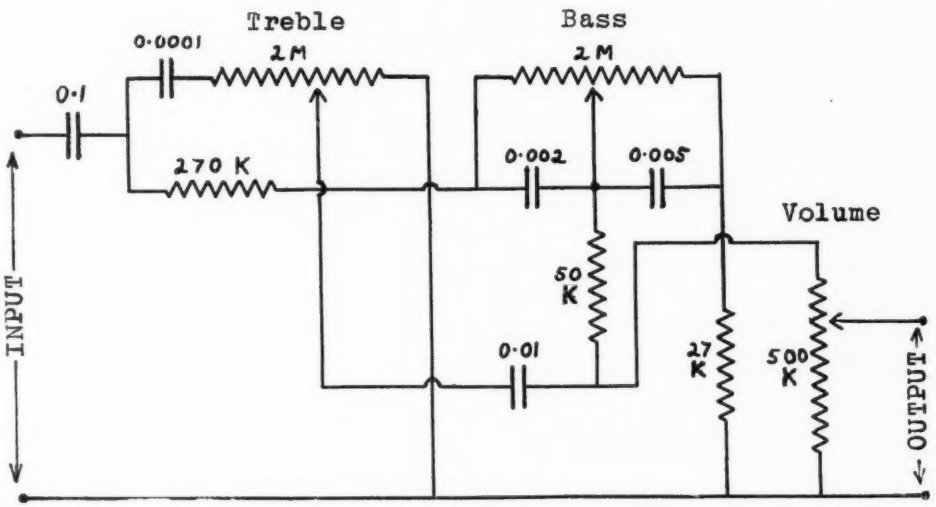

Fig. 2.—Full diagram of the filter circuit showing treble, bass, and volume controls. Resistances in thousands of ohms (K) and megohms (M). Capacities in fractions of a microfarad.
Input: direct from anode of second triode amplifier stage, anode load 100 K.
Output: direct to grid of subsequent stage.

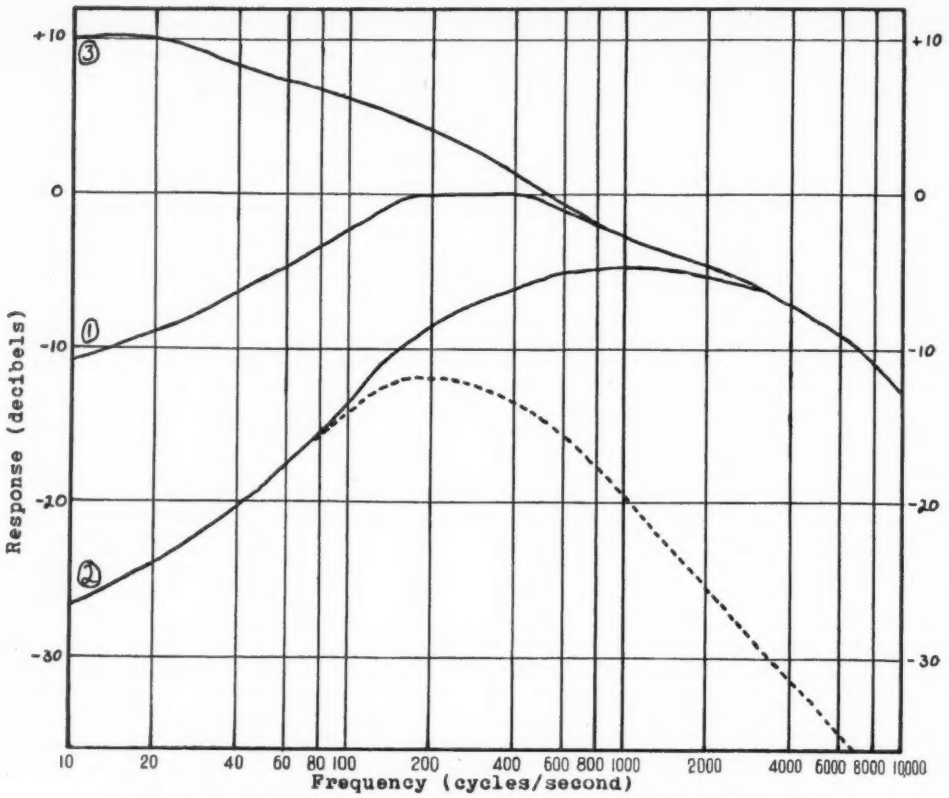

FIG. 3.—Frequency-response curves of amplifier to show the effect of the bass control.

Full curves: treble control central.

(1) Bass control also central.
(2) Bass control set at minimum.
(3) Bass control set at maximum.

Broken curve: both controls set at minimum.

frequency response. The published performance curve indicates a response that is practically independent of frequency down to 35 c/s, with no significant resonances.

There is a slight tendency to boom at the first heart-sound, and this is in most cases the factor that limits the maximum volume consistent with good reproduction.

Connection to the loud-speaker is made by means of 20 feet of twin flex, with a jack which is plugged into the main amplifier box. An extension of 35 feet of twin flex is available, with a jack socket at one end and a plug at the other. Each socket is arranged to leave a 15-ohm load across the output when the corresponding plug is removed, so that there is no danger of leaving the output transformer unloaded.

RESULTS

The equipment gives a very close approach to the effect of auscultation with a stethoscope, in a quiet room large enough for twenty people. For auscultation over the præcordium the apparent loudness cannot usefully be increased much above that heard with a stethoscope because distortion of the sounds begins to occur. A variety of pathological murmurs have been listened to, and these as well as the normal sounds are satisfactorily heard. On the whole, very

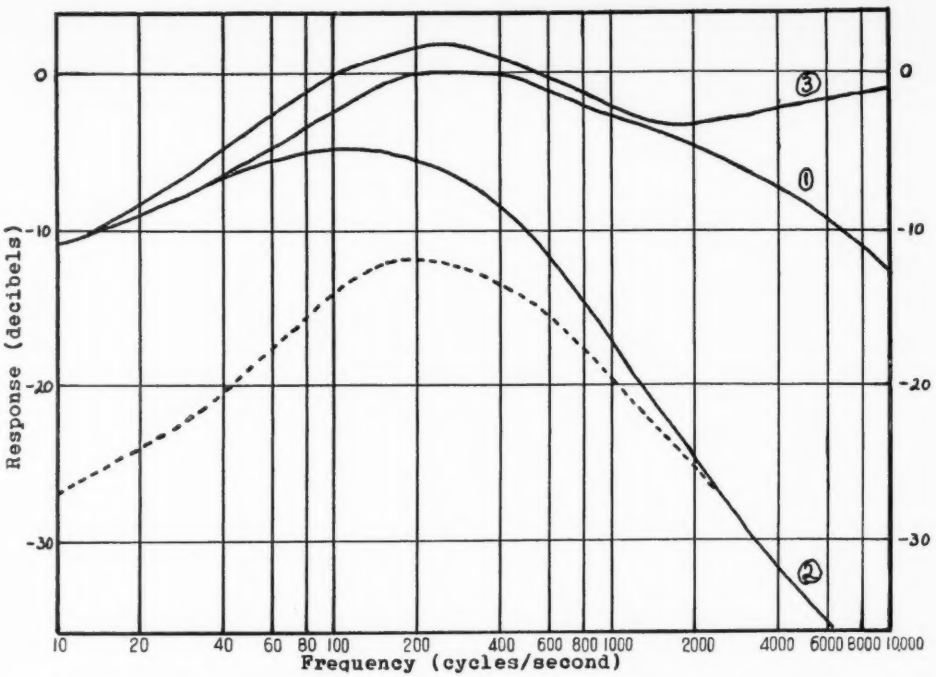

FIG. 4.—Frequency-response curves of amplifier to show the effect of the treble control.

Full curves: bass control central.

(1) Treble control also central.
(2) Treble control set at minimum.
(3) Treble control set at maximum.

Broken curve: both controls set at minimum.

faint murmurs are not more easily picked up with the loud-speaker than with a stethoscope, but simultaneous auscultation will allow each student to listen for a much longer time than he would otherwise be able to do, and so increase his chances of picking up a difficult murmur.

For auscultation of breath sounds the volume can be considerably increased without distortion, and both normal and pathological sounds are picked up much more easily than with a stethoscope. The volume can then of course be reduced to simulate a stethoscope more exactly.

SUMMARY

The problems of electrical amplification of heart sounds and of group auscultation are discussed both theoretically and with reference to previous work.

A portable equipment is described which is believed to be suitable for teaching groups of at least twenty students. This consists of a crystal microphone, an electrical amplifier, and a loud-speaker, which have been arranged to give an effect that simulates very closely auscultation with a stethoscope.

The amplification, and the high- and low-frequency response of the amplifier, can be easily and silently controlled during auscultation. The relevant frequency response curves are given.

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THE EFFECT OF ADENOSINE TRIPHOSPHATE ON THE ELECTROCARDIOGRAM OF MAN AND ANIMALS

BY

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The increasing importance of adenosine triphosphate (*ATP*) in the field of biochemistry demands a close study of its pharmacological properties. Earlier work on the lower nucleotides and nucleosides derived from *ATP* showed that these compounds have important effects on the cardiovascular system. Now that large amounts of the higher derivatives, such as *ATP*, have become available, it has been shown that the action of these substances is not confined to the cardiovascular system but affects all the organs of the body (Green and Stoner, 1949). Although the effect of these compounds on the heart has been studied in some detail by Drury and his school (1936), their electrocardiographic observations were almost entirely confined to the lower members of the series. In the present paper we propose to describe the effects of *ATP* on the electrocardiogram of man and animals. The cardiographic method is the only satisfactory one available for the study of changes in cardiac rhythm in man. We have also applied this method to the study of the cardiac effects of *ATP* in animals in order to determine the effects of doses higher than those that would have been justifiable in man and also to analyse these actions by procedures impracticable clinically. The observations in animals will be reported first, then those in the human subjects, and finally the conclusions arrived at from the combined study.

I. Animal Experiments

Early work on the effect of adenosine and its derivatives on the electrocardiogram has been well reviewed by Drury (1936). It has been shown that these substances affect the conducting system, causing sinus slowing and A-V block. In most animals the main effect is upon the S–A node but in the guinea pig the A-V node seems more sensitive to their action. It will be seen that the action of *ATP* is on the whole similar to that of the lower compounds. The further actions of *ATP* on the cardiovascular system have been described by us elsewhere (Green and Stoner, 1949).

Methods. Experiments were performed on 10 cats and 11 guinea pigs under pentobarbitone sodium (nembutal) anæsthesia. The electrocardiogram was recorded with a Sanborn Viso-cardiette. In the cat the pressure in the carotid artery was determined with a mercury manometer and respiration recorded by a tambour attached to a tracheal cannula. Artificial respiration was used in the majority of the guinea pig experiments. All injections were given into the external jugular vein and washed in with 1·5 ml. 0·9 per cent sodium chloride from a burette. The time of the injection was 1 sec. Both the sodium and magnesium salts of *ATP* were used in the animal experiments, the solutions being prepared from *BaATP* (Boots) as described elsewhere (Green and Stoner, 1949). In the observations on man the magnesium salt was used. The purity of the *ATP* was checked by chemical analysis and found to be not less than 98 per cent. The adenosine used was obtained from British Drug Houses Ltd.

Results

Guinea Pig. The effect of *ATP* on the conducting system of the guinea pig heart was followed in leads I and II. Two dosage levels were used—0·5 mg. and 1·0 mg. *MgATP* per kg. body weight. With the smaller dose the effect on the heart commenced almost immediately after the injection and lasted about 21 seconds, reaching a maximum in 6 to 9 seconds. The first effects were on the sinus rate and the P–R interval. The sinus rate was reduced by about 18 per cent and the P–R interval

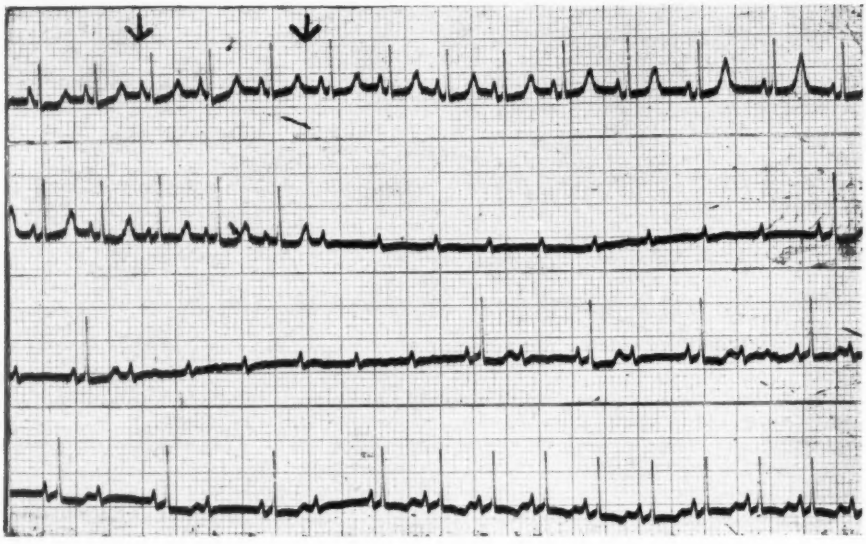

FIG. 1.—To be read from left to right and from above downwards. The effect of 0·5 mg. *MgATP* per kg. body wt., given intravenously, on the electrocardiogram (lead II) of the guinea pig under pentobarbitone (nembutal) anæsthesia. The beginning and end of the injection indicated with arrows. Shows sinus slowing followed by ventricular arrest and 2: 1 A-V block.

1 mV=1·6 cm. 1 sec.=2·5 cm.

was increased from an average control value of 0·06 to between 0·09 and 0·12 second. At the height of the effect *ATP* exerted a much greater action on the A-V node than on the S–A node and the ventricular beat was completely suppressed for periods of up to 3 seconds. Ventricular beating then returned with 2:1 heart block progressing to normal rhythm (Fig. 1).

Despite these marked changes in rhythm the form of the complexes showed little change. The only constant alterations seen were some depression of the P–Q interval giving a spiky appearance to the P waves and increased amplitude of the T waves.

After the larger dose of *ATP* the effect attained a maximum at about the same time after the injection and persisted for about 30 seconds. The sequence of events was as before but both the sinus slowing and prolongation of the P–R interval were more marked. The sinus rate was reduced by a maximum of about 36 per cent and the P–R interval was prolonged until at the height of the effect the ventricular beat was suppressed for 6 to 9 seconds. On occasions this was accompanied by atrial asystole. Recovery occurred as before with varying grades of heart block.

Changes in the configuration of the complexes were commoner after the larger dose of *ATP*. Increased amplitude of the T wave was evident and low voltage QRS complexes and extrasystoles were also seen. These extrasystoles arose from a focus close to, but below, the A-V node. Occasional abnormalities which were seen, usually during the recovery period, were inversion of the P wave, auricular fibrillation, nodal rhythm, and displacement of the S–T segment.

When adenosine was given in equimolecular amounts it had the same effect on cardiac rhythm as *ATP*. Section of the vagi in the neck did not alter the response to *ATP* or adenosine.

Cat. The effect of *ATP* on the electrocardiogram (lead II) of the cat was studied after the intravenous injection of 1·0 mg. and 2·0 mg. *MgATP* (0·3–0·5 and 0·7–1·0 mg. per kg. body weight). The effects observed differed somewhat from those in the guinea-pig and more closely resembled those to be described in man.

The main effects after the smaller dose of *ATP* were sinus bradycardia and lengthening of the P–R interval. The degree of sinus slowing varied but at the height of the effect, about 10 seconds after

injection, the sinus rate was usually decreased by about 50 per cent. The effect persisted for a further 10 to 20 seconds by which time the rate had returned to normal. The P–R interval increased from 0·06 to 0·09 second at the height of the effect. The P–Q interval was depressed and changes constantly occurred in the T wave. In the majority of experiments the T wave was increased in amplitude during the first 10 seconds after the injection. Sometimes this change persisted for as long as 42 seconds and was accompanied by alterations in the level of the S–T segment (Fig. 2). In other experiments, during the later stages of the *ATP* action, the T waves were depressed and then inverted.

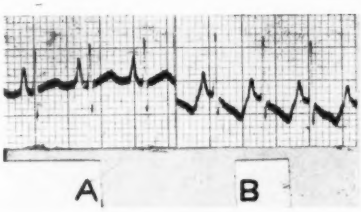

FIG. 2.—Segments of the electrocardiogram (lead II) record immediately before (A), and 15 sec. after (B), the intravenous injection of 2·0 mg. *MgATP* into a cat (3·0 kg. body wt.) under pentobarbitone (nembutal) anæsthesia, showing the depression of the S–T segment.
1 mV = 1·6 cm. 1 sec. = 2·5 cm.

Similar but more marked changes occurred after the larger dose (Fig. 3). Here the P–R interval was increased from an average control value of 0·07 to 0·11 second. Sinus bradycardia, which was still the main effect, was more pronounced sometimes leading to complete asystole; in one experiment there was complete asystole for 6 seconds with ventricular asystole for 11 seconds. The maximum effect occurred about 10 seconds after the injection and was characteristically heralded by a run of about four extrasystoles (Fig. 4) arising from a focus close to, but below, the A-V node. The T wave changes were of the same type as before but were more evident after these larger doses.

Previous work has shown that the vagus is concerned in the cardiovascular response to *ATP* in the cat (Bielchowsky, Green, and Stoner, 1946). In this animal section of the vagi in the neck or atropinization diminished the effect of *ATP* on both the blood pressure and the heart, but the blood pressure changes were much less affected than one would have expected from the changes in the cardiac response (Fig. 5). For instance, in one experiment where the depressor response to 2·0 mg. *MgATP* was 35 mm. Hg. before vagal section, the P–R interval was prolonged from 0·06 to 0·10 second, and the sinus rate slowed from 180 to 60 beats a minute with complete A-V dissociation for 3 seconds. After vagal section the same dose only prolonged the P–R interval very slightly, from 0·06 to 0·08 second, and slowed the sinus rate only from 160 to 140 beats a minute without dissociation; nevertheless the blood pressure fell by as much as 22 mm. Hg. Although inactivation of the vagi greatly reduced the effect of *ATP* on cardiac rhythm it did not alter its action on the configuration of the complexes nor prevent the appearance of extrasystoles.

Prostigmine had the opposite effect to vagal section and greatly potentiated the action of *ATP* on cardiac rhythm in the cat (Fig. 6). In a normal cat 2·0 mg. *MgATP*, injected intravenously, lengthened the P–R interval from 0·08 to 0·12 second, and produced complete asystole for 3 seconds. In the same cat, after intravenous injection of 0·125 mg. prostigmine, the same dose of *MgATP* lengthened the P–R interval from 0·11 to 0·14 second and produced complete asystole for 18 seconds followed by a slow return to normal beating. At the same time the depressor response was increased. This effect of prostigmine could be prevented by vagal section.

In the cat the rate changes produced by *ATP* were not reproduced by equimolecular amounts of adenosine until after section of the vagi when the effects were similar.

Effect of Magnesium. The influence of intravenous magnesium sulphate on the response to *ATP* was tested in both guinea pig and the cat in view of previous work on the effect of this ion on nucleotide action (Green and Stoner, 1944; Bielchowsky, Green, and Stoner, 1946). The alteration in the response after Mg was more easily interpreted in the guinea pig since the vagus is not implicated in that animal. As shown in Table I, the effect of intravenous magnesium sulphate was to increase the effect of *ATP* on the cardiac rhythm. Mg^{++} had a similar influence on the action of *ATP* on the cardiac rhythm of the cat but in that animal the effect was complicated by the anæsthetic action of Mg^{++} on the vagus. Small doses of Mg^{++}, however, increased the effect of *ATP* on the P–R interval and the duration of the effect. The prolongation of the action of *ATP* on cardiac rhythm was not the only effect of Mg^{++} on the *ATP* response, since it also prevented the appearance of extrasystoles.

Effect of Antimalarial Drugs. Raventós (1948) has recently postulated that there is an antagonism between adenosine and the antimalarial group of

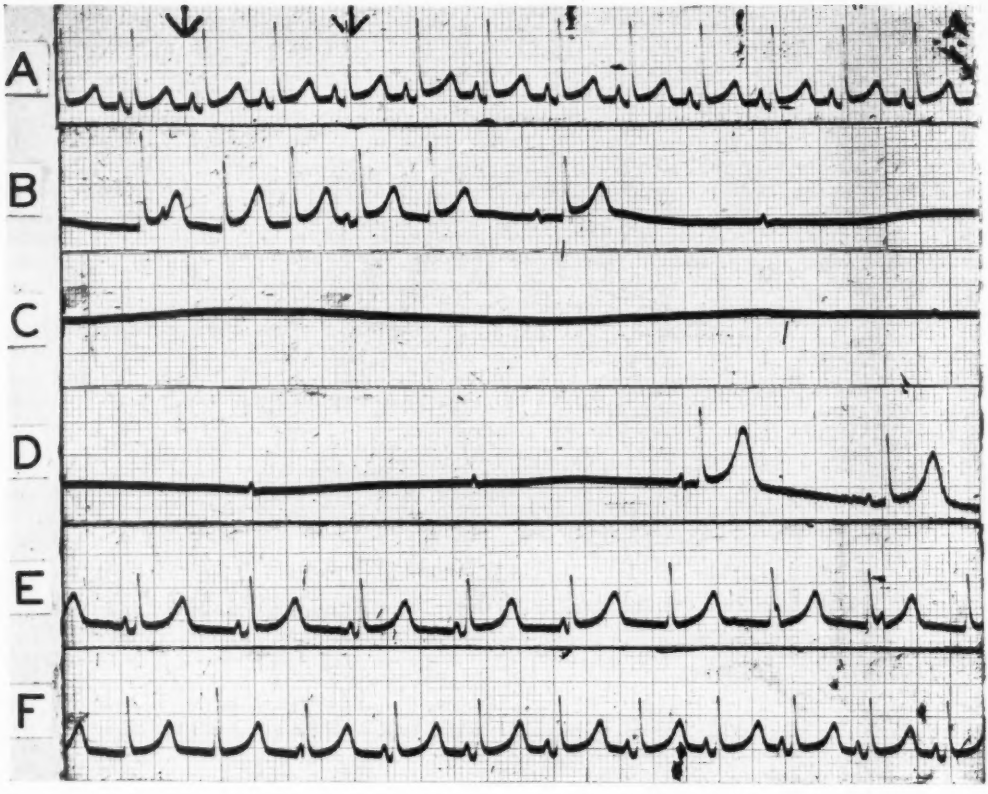

FIG. 3.—To be read from left to right and from above downwards. The effect of 2·0 mg. *MgATP* given intravenously on the electrocardiogram (lead II) of the cat (2·9 kg. body wt.) under pentobarbitone anæsthesia. The beginning and end of the injection is indicated with arrows. Shows sinus slowing, ventricular asystole and complete asystole with nodal rhythm during the recovery period.

(A) 0–5 sec.
(B) 11–16 sec.
(C) 16–22 sec.
(D) 22–27 sec.
(E) 45–50 sec.
(F) 55–60 sec.

1 mV = 1·6 cm. 1 sec. = 2·5 cm.

drugs since he found that the cardiac effects of adenosine were less after the previous administration of quinine, mepacrine, pamaquin, and paludrine. In the guinea pig heart lung preparation he found that paludrine, added directly to the circulating blood, did not antagonize the action of adenosine but that the blood of guinea pigs treated with paludrine did have this effect.

In part we have been able to confirm these findings. In the cat, the intravenous or intramuscular injection of quinine sulphate (25 mg. per kg. body weight) does decrease the effect of *ATP* on the heart and blood pressure. In the guinea pig also, quinine sulphate (15 mg. per kg. body weight) decreases the effects of adenosine and *ATP* on the heart. In our hands paludrine hydrochloride has behaved differently and when doses in the therapeutic range have been given intravenously over a period of half an hour no change was observed in the electrocardiographic response to *ATP* in the cat or guinea pig. It was only when the dose was raised to the limits of tolerance (60 mg. per kg. body weight) that any alteration in the response was observed and then the changes were only slight and equivocal.

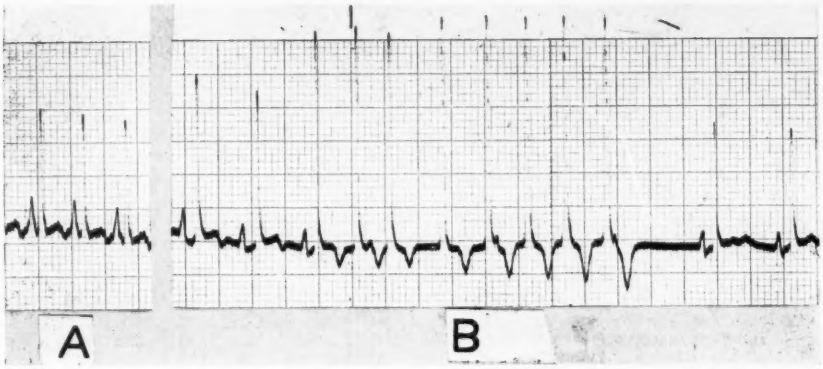

FIG. 4.—Segments of the electrocardiogram (lead II) record immediately before (A), and 5 sec. after (B), the intravenous injection of 2·0 mg. *MgATP* into a cat (2·1 kg. body wt.) under pentobarbitone (nembutal) anæsthesia. Shows the characteristic run of nodal extrasystoles preceding the full action of the *MgATP*.

1 mV=1 c.cm. 1 sec.=2·5 cm.

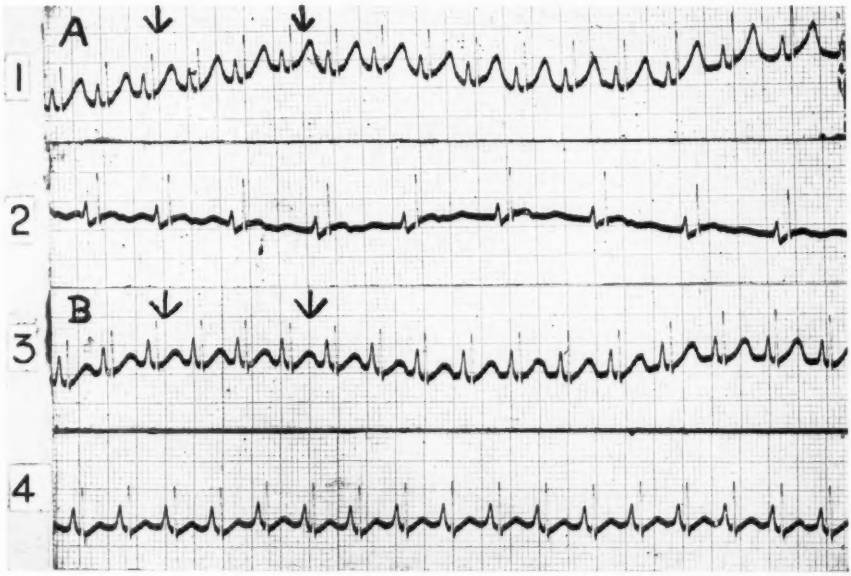

FIG. 5.—To be read from left to right and from above downwards. The effect of 2·0 mg. *MgATP* given intravenously on the electrocardiogram (lead II) of a cat (2·7 kg. body wt.) under pentobarbitone (nembutal) anæsthesia, (A) before, and (B) after, the intravenous injection of 0·75 mg. atropine sulphate per kg. body wt. The beginning and end of the injection of *MgATP* indicated with arrows.

(1) 0–5 sec. (2) 11–16 sec. (3) 0–5 sec. (4) 11–16 sec.

Shows the decrease in the degree of sinus slowing produced by *MgATP* after paralysis of the vagus.

1 mV=1·6 cm. 1 sec.=2·5 cm.

TABLE I

THE EFFECT OF INTRAVENOUS MAGNESIUM SULPHATE ON THE CARDIAC RESPONSE TO *ATP* IN THE GUINEA PIG

Dose No.	Duration of effect (sec.)	P–R interval (sec.)		Sinus rate Beats per minute		Ventricular rate Beats per minute	
		Before Injection	After Injection	Before Injection	After Injection	Before Injection	After Injection
1	18	0·06	0·09	220	180	220	80
2	18	0·06	0·09	200	180	200	100
3	31	0·11	0·16	120	60	120	20
4	3[illegible]	0·10	0·18	120	80	120	0

The table shows the effect of successive doses of *MgATP* (0·5 mg. per kg. body weight) on the P–R interval, and sinus and ventricular rates, before and after intravenous doses of magnesium sulphate.

Between doses No. 2 and 3, 3·0 ml. $MgSO_4$ 0·154 M given i.v. and between doses No. 3 and 4, 2·0 ml. $MgSO_4$ 0·154 M i.v.

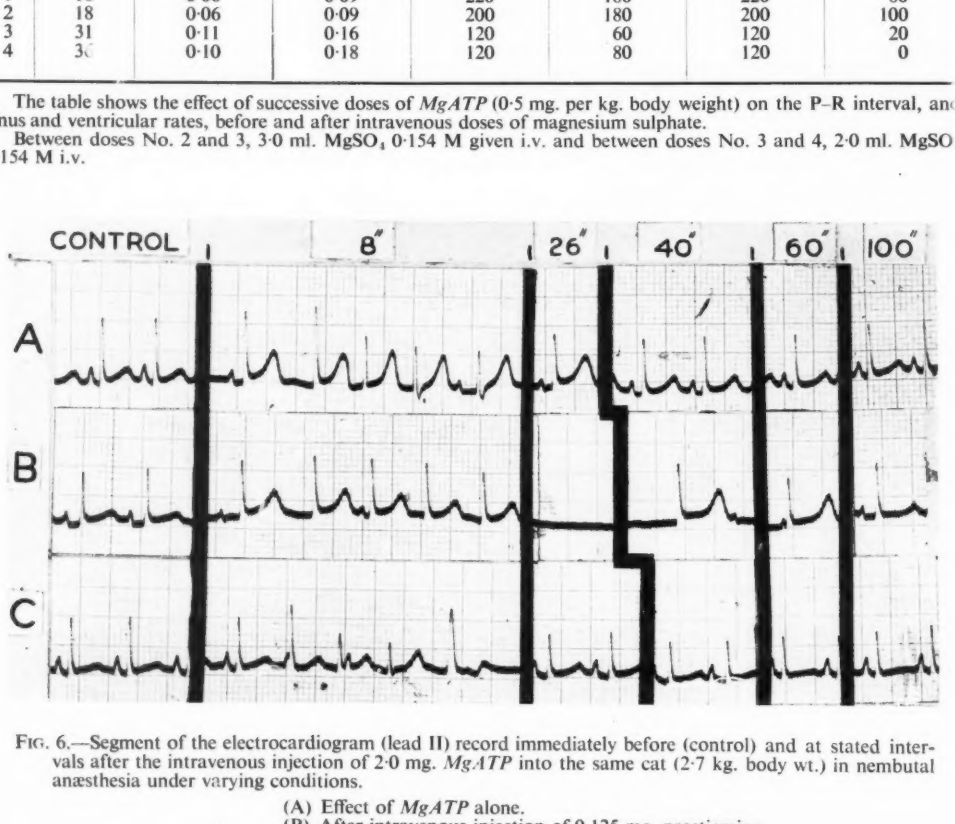

FIG. 6.—Segment of the electrocardiogram (lead II) record immediately before (control) and at stated intervals after the intravenous injection of 2·0 mg. *MgATP* into the same cat (2·7 kg. body wt.) in nembutal anæsthesia under varying conditions.

(A) Effect of *MgATP* alone.
(B) After intravenous injection of 0·125 mg. prostigmine.
(C) As for (B) except that both vagi have been divided.

Shows the great increase in the effect of *ATP* after prostigmine administration, which is prevented by division of the vagi.

1 mV = 1·6 cm. 1 sec. = 2·5 cm.

II. OBSERVATIONS ON HUMAN SUBJECTS

The effect of adenyl compounds on the human heart has been comparatively little studied. Honey, Ritchie, and Thomson (1930) showed that adenosine could produce heart block in healthy men and von den Velden (1932) that adenylic acid would give bradycardia. Richards (1934*a*) studied the effects of both adenylic acids and adenosine on the blood pressure and electrocardiogram. He concluded that the blood pressure is unaffected but that in some individuals heart block can be produced by

ither compound. Stoner and Green (1945) using he sodium and magnesium salts of *ATP* produced rise of pulse rate with small doses and a rise followed by a large fall with large doses. Electrocardiograms were not taken but heart block was suspected in one case. The systolic blood pressure was raised during the period of tachycardia and fell slightly during the time when the pulse was slowing. Arteriolar dilatation occurred with a consequent rise of skin temperature.

ATP in the Treatment of Rheumatoid Arthritis. Lövgren (1945) has claimed that *ATP* has a beneficial effect on cases of rheumatoid arthritis. "Adynol," a crude preparation containing 50 to 60 per cent *ATP*, was given by intravenous injection in doses of 30 to 45 mg. or by intramuscular injection in doses of 7·5 to 30 mg. We decided to treat a series of cases with a purer preparation of *ATP* and at the same time to study the effect of this substance on the cardiovascular system.

The results of treatment of rheumatoid arthritis were most disappointing. Courses of daily injections of *MgATP* in doses of 15 to 30 mg. were given for periods up to three months to 15 patients. Several cases improved subjectively but we could not convince ourselves that there was any change in the degree of disability that would not have been obtained by simple rest in bed and physiotherapy. There was no significant alteration in the erythrocyte sedimentation rate.

Since, as will be shown, *MgATP* has a profound effect on the conducting system of the heart and since it was desired to give to each patient the maximum tolerated dose, very frequent electrocardiographic observations were made on each case. These will now be reported.

Plan of Investigation. Seven patients (6 male and 1 female), all with normal hearts, were chosen from the 15 treated for arthritis and were observed specifically for electrocardiographic changes immediately after injection. The patient rested comfortably on a couch, and control blood pressure readings and cardiograms were taken. *MgATP* was injected intravenously, taking 6 to 12 seconds over the injection. Blood pressure readings were taken at 15-second intervals, until the figures returned to pre-injection levels. Cardiograms were taken at the same time as the injection and continued for 1 minute and then for 10 seconds at half-minute intervals for a further minute. Small doses of 5 mg. were used initially on each patient and gradually increased by 5 mg. at each injection up to the maximum tolerated dose which varied from 15 to 40 mg. (0·21–0·57 mg. per kg. body weight). In all, 100 tracings were obtained in this manner from the 7 patients selected.

Effects of Injection

(1) *Subjective.* These were remarkably constant with doses above 10 mg. Ten to fifteen seconds after starting the injection, the subject noted a sharp taste in the mouth, which was followed by hyperpnœa, cough, and obvious flushing of the face with a brief sensation of faintness and throbbing in the head. All these effects had disappeared by the end of the first minute and were much less marked if the injection was made slowly.

(2) *Blood pressure.* Thirty observations were made on four cases with doses above 10 mg. A fall of blood pressure invariably occurred, the maximum being 100 mm. Hg with doses of 35–40 mg. and was usually greatest about 15 to 20 seconds after the beginning of the injection. The blood pressure recovered rapidly so that two minutes later it was at or above the pre-injection level. It is hardly surprising that very low readings were obtained in cases in which asystole or pronounced bradycardia occurred but in several instances with doses giving only sinus slowing, significant falls of pressure were recorded which we attributed to arteriolar dilatation. In general, the fall in systolic pressure was greater than in diastolic pressure but the latter is difficult to determine accurately in observations of this type. The fall in systolic pressure was considerably greater than that previously recorded (Stoner and Green, 1945).

(3) *Changes in the Electrocardiogram.* Lead II was used throughout the observations.

The effects of a given dose differed greatly in different patients but in the same patient, the response was sufficiently constant to enable variations produced by other procedures to be assessed. We did not observe the development of tolerance. In our observations on the effects of drugs, we always made at least one control observation immediately before giving the drug and one after the effect of the drug had worn off. We also always used samples of *ATP* from the same batch.

Small doses (5–15 mg.) of *MgATP* produced a sinus tachycardia preceded by a short period of sinus slowing. Larger doses (15–30 mg.) gave marked sinus slowing and always affected the conducting tissues producing first or second degree A-V block (Fig. 9A and C). Wenckebach periods were often observed (Fig. 10A). Maximum doses (30–40 mg.) produced similar changes of greater intensity with an increase in the duration of heart block and in the number of dropped beats. Ventricular standstill (Fig. 7) and complete asystole were observed in two patients. These effects are similar to those seen in the guinea pig (Fig. 1). The results in Case 1 are summarized in Table II.

With the doses used, changes in the shape of the

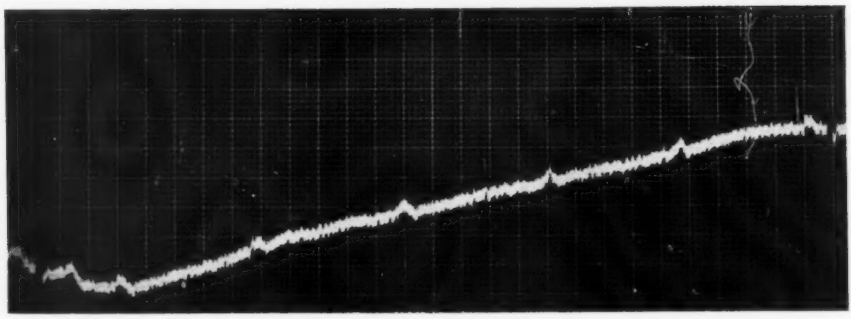

FIG. 7.—Case IV. Effect of intravenous injection of *MgATP* on the electrocardiogram (lead II). Shows ventricular standstill for 5·5 sec. occurring 14 sec. after injecting 19 mg. *MgATP*.
1 mV=1 cm. 1 sec.=2·5 cm.

TABLE II
RESULTS OBTAINED IN CASE I

Dose of *MgATP* (Mg.)	Other drugs	Maximum increase in P–R interval (Sec.)	Wenckebach phenomenon	Number of dropped beats	Duration of block (Sec.)	Sinus slowing	Remarks
30	—	0·20	+	1	6	+	Typical single observation
30	—	0·14	—	1–2	8	+	Mean of 7 observations
30	After 400 mg. mepacrine orally	0·05	—	0	2·5	+	
30	After 100 mg. paludrine orally	0·22	—	1	9	+	
35	—	0·28	+	1	9	+	
35	—	0·16	+	1–2	6	+	Mean of 5 observations
35	After 1·2 mg. atropine intravenously	0	—	0	0	+	
35	After 2·4 mg. atropine intravenously	0	0	0	0	+	
40	—	0·14	+	1	10	+	
40	—	0·16	+	1–0	7·5	+	Mean of 2 observations
40	After 1 g. quinidine sulphate orally	0·06	—	1	2	++	
40	After 3 g. quinine hydrochloride orally	0·04	—	0	0	++	

Table II shows the effects of *MgATP* on the heart and the effects of mepacrine, paludrine, quinidine, quinine, and atropine on the cardiac response to *MgATP*.

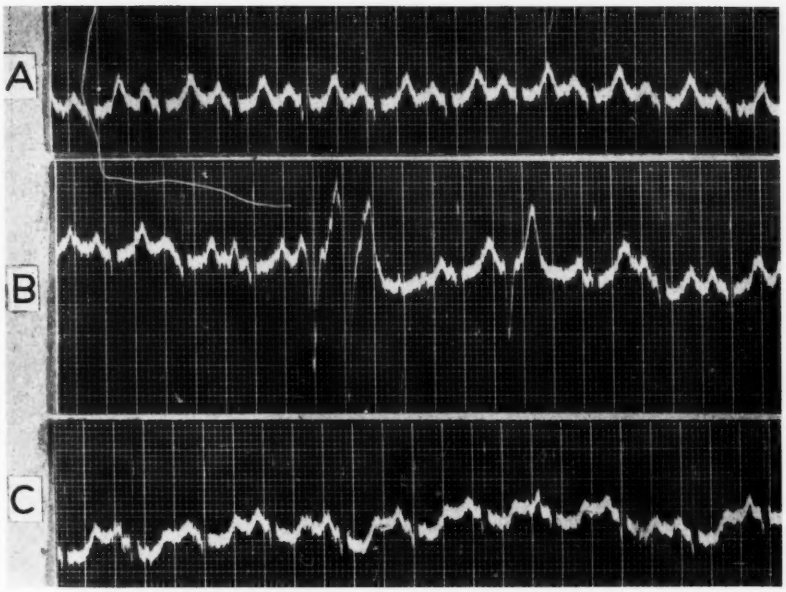

FIG. 8.—Case VII. Effect of intravenous injection of *MgATP* on the electrocardiogram (lead II).

(A) Before injection showing sinus tachycardia.
(B) 16 sec. after injection of 15 mg. *MgATP* showing 3 ventricular extrasystoles.
(C) 26 sec. after the same injection, showing depression of the S–T segment.

1 mV=1 cm. 1 sec.=2·5 cm.

complexes were not produced as consistently as in the observations on animals. In Case 3, with doses of 20 to 30 mg., the P wave was depressed, a small Q wave appeared and the T wave became isoelectric or inverted. In Case 7, with doses of 10 to 15 mg., premature ventricular contractions were observed and later the S–T interval was significantly depressed. Heart block did not occur in this case with these doses and it was thought inadvisable to increase them. The curves from this case which were obtained on three separate occasions resemble closely those obtained in the cat (compare Fig. 2 and 8).

Comparison of MgATP and Adenosine. The effects of adenosine and *MgATP*, given in equimolecular amounts, were compared in 2 subjects (Cases 1 and 2). It was found that although adenosine produced the same type of change in cardiac rhythm as *MgATP* it was not as active.

OBSERVATIONS ON THE RESPONSE TO *ATP* AFTER THE INJECTION OF OTHER DRUGS

These observations fall into two main groups. Firstly an attempt was made to see whether the effects of magnesium sulphate and of vagal inactivation by atropine on the response to *ATP* in man were the same as those we had encountered in animals. The effects of adrenaline and quinidine were also investigated, the former because it is known to facilitate conduction down the bundle (Wiggers, 1927) and the latter because it might have been expected to increase the degree of conduction defect as in clinical cases of heart block (Lewis, 1925). Secondly, we investigated the effect of various antimalarial drugs on the response of the human heart to *ATP* in view of the animal experiments of Raventós which we had partially confirmed.

Magnesium Sulphate. This substance was given intravenously in a doze of 1·6 g. $MgSO_4$. 7 H_2O (8 ml. of 20 per cent solution) to 2 subjects, 7 to 10 minutes before the injection of *MgATP*. In both, there was a definite increase in the degree of heart block produced by *MgATP*. The results therefore resemble those obtained in animals.

Adrenaline. Injections of *MgATP* were given to 2 subjects 5 minutes after an intramuscular injection

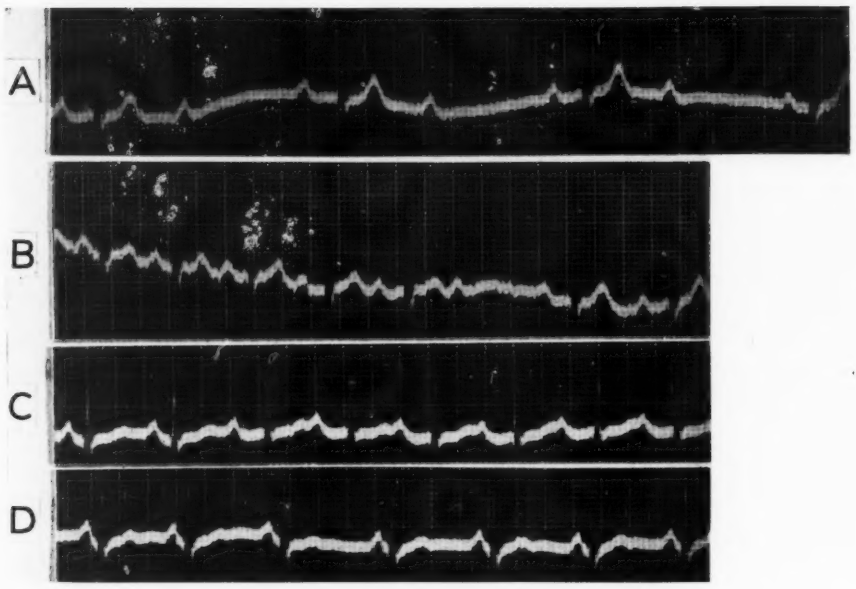

FIG. 9.—Effect of *MgATP* on the human electrocardiogram before and after intravenous injection of atropine.

(A) Case IV, 15 sec. after injection of 17 mg. *MgATP*.
(B) Case IV, 15 sec. after injection of 17 mg. *MgATP*. Five minutes previously 2·5 mg. atropine sulphate had been given intravenously.
(C) Case I, 15 sec. after injection of 35 mg. *MgATP*.
(D) Case I, 18 sec. after injection of 35 mg. *MgATP*. Five minutes previously 1·2 mg. atropine sulphate had been given intravenously.

Both cases show reduction in the degree of heart block due to *MgATP* after atropine administration. Sinus slowing is still seen.

1 mV=1 cm. 1 sec.=2·5 cm.

of 0·5 ml. 1: 1000 adrenaline hydrochloride and to 1 subject after 1·0 ml. The number of dropped beats and the duration of the block was reduced in each instance.

Atropine. After control observations, 5 subjects were given atropine sulphate intravenously in doses usually considered sufficient to produce complete vagal paralysis. When the heart rate had risen to a stationary level, *MgATP* was given. Sinus slowing still occurred, but in two instances second degree A-V block was completely prevented. In the other observations the degree and duration of heart block was much less (Fig. 9 and Table II).

Quinidine. Two subjects (Cases I and VI) received 1 g. of quinidine sulphate in divided doses, the last dose of 0·2 g. being given half an hour before the injection of *MgATP*. The increase in P–R interval and the duration of heart block were significantly less than in the control observations (Fig. 10 and Table II). The degree of sinus slowing was the same.

Antimalarial drugs. 1. *Quinine*. Three grammes of quinine hydrochloride were given orally over 3 days to 4 subjects (Cases 1, 2, 4, and 6), the last dose being administered half to two hours before the injection of *MgATP*. The effects were similar to those obtained using quinidine and in one case A-V block was almost completely prevented (Fig. 10E and Table II).

2. *Mepacrine*. Three subjects (Cases 1, 2, and 6) received 0·4 g. mepacrine hydrochloride by mouth over thirty-six hours, the last dose of 0·2 g. being given two hours before the injection of *MgATP*. The degree and duration of heart block were significantly less than in control observations (Fig. 10B and Table II).

3. *Paludrine*. Three subjects (Cases 1, 2, and 6) were given 100 mg. paludrine hydrochloride by

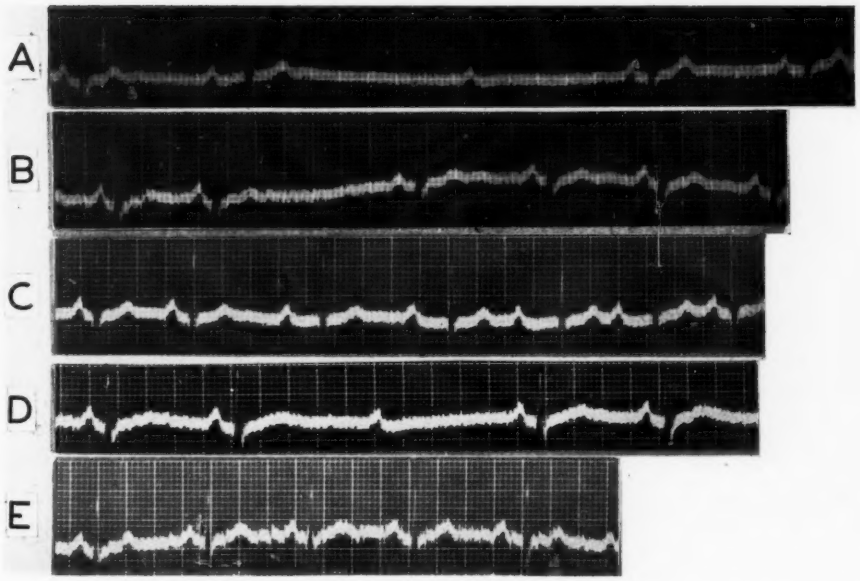

FIG. 10.—Case I. Effect of mepacrine, quinidine, and quinine on the response to the intravenous injection of *MgATP* (lead II).

(A) Control, 17 sec. after injection of 30 mg. *MgATP*. Normal P–R interval for this case lay between 0·16 sec. and 0·18 sec.
(B) Effect of mepacrine (for dosage, see text) : 18 sec. after injection of 30 mg. *MgATP*.
(C) Control; 17 sec. after injection of 40 mg. *MgATP*.
(D) Effect of quinidine (for dosage, see text): 16 sec. after injection of 40 mg. *MgATP*.
(E) Effect of quinine (for dosage, see text): 17 sec. after injection of 40 mg. *MgATP*.

Shows the reduction in the effect of *ATP* after certain antimalarial drugs.

1 mV=1 cm. 1 sec.=2·5 cm.

mouth and one (Case 4) 200 mg. three hours before injection of *MgATP*. No reduction in the degree of block was noted. Indeed, in Case 4 the block persisted much longer than in control observations. We thought it inadvisable to investigate the effects of higher doses, because of toxic symptoms produced by the dosage given to Case 4.

DISCUSSION

These observations show that *ATP* has a profound effect on the conducting system of the heart causing changes in cardiac rhythm similar to those described for adenosine and muscle adenylic acid by Drury and Szent-Gyorgyi (1929). The action is essentially a depression of normal function with sinus slowing, prolongation of the P–R interval and the appearance of heart block. With sufficiently large doses this A-V block may be complete and complete asystole can also occur. In man these effects were often followed by a short period of sinus tachycardia but the second phase of sinus bradycardia described by Drury and Szent-Gyorgyi (1929) was seldom seen in our observations, perhaps because we used smaller doses. With very small doses of *MgATP*, sinus tachycardia was (sometimes) the only effect produced. For the most part the effect of *ATP* was similar in the three species studied but there were certain interesting minor differences. Drury (1936) has emphasized that the site of the main action of the adenyl compounds differs in different species. As with the lower compounds, the main action of *ATP* in the guinea pig is upon the A-V node whereas in man and the cat, especially in the latter, the main effect is upon the S–A node. An illustration of this is the more frequent occurrence of complete asystole in the cat than in the guinea pig.

McDowall (unpublished report to the Medical Research Council, 1944) first pointed out that the vagi participated in the cardiovascular response to *ATP* in the cat and this has been fully confirmed by

us both here and elsewhere (Bielchowsky, Green, and Stoner, 1946; Green and Stoner, 1949). We found that amongst the common laboratory animals this reaction was only seen in the cat and that in this animal it was only *ATP* which acted in this way. The present studies, in addition to giving some information on the efferent mechanism of this reflex, also show that the vagi are similarly involved in man. Experiments on the vagotomized cat indicate that the sinus bradycardia after *ATP* is in part due to its action through the vagi. In man, with the vagi paralysed by atropine, the reduction in the degree of sinus slowing was not so marked but the elimination of the A-V block was very striking.

Direct comparison of the changes in cardiac rhythm produced by equimolecular amounts of adenosine and *ATP* showed that the effects were the same in the guinea pig but not in the cat or man, i.e. in the two species where the vagus is involved. A similar effect was, however, seen in the cat after the vagi had been divided. These findings are in agreement with those on the isolated perfused rabbit's heart (Green and Stoner, 1949) which showed that the effect of these compounds on the conducting system is essentially due to their adenosine content.

Alterations in the cardiac rhythm are not the only changes seen after the injection of *ATP*. Various other changes occurred, notably ventricular extrasystoles and displacement of the S–T segment, which are best attributed to a direct action on the myocardium. This effect is not seen after adenosine for as Drury (1932) and Green and Stoner (1949) have shown it is only the phosphorylated derivatives which possess this action.

That *ATP* has this action on the myocardium may be of some practical importance. Adenosine and muscle adenylic acid, often mixed with other substances in the form of tissue extracts, have been widely used in the treatment of cardiac and peripheral vascular disease. The alleged beneficial effects have been attributed to vasodilatation of the coronary and peripheral vessels and to a direct action on the myocardium. It seems improbable that, in the doses given and using the routes of administration advised, beneficial results would be likely to ensue. But, in view of the greater general activity and more definite role of *ATP* in muscle metabolism, it is probable that attempts will be made to use this substance in the therapy of cardiovascular disease. In view of the ectopic beats and alterations in the S–T segment observed by us this would seem unjustifiable. If it is given in the treatment of other types of disease it should be given by slow intravenous injection or intramuscularly. Unfortunately, when given by the latter route the dose must be large and absorption is irregular.

It is of great interest that the cardiac effects of *ATP* are capable of being influenced by the previous administration of other substances, one of the most important of which is Mg^{++}. The striking effect of this ion in increasing the shock-inducing action of *ATP* and altering its action on the cardiovascular system have been dealt with elsewhere (Green and Stoner, 1944; Bielchowsky, Green, and Stoner, 1946). The electrocardiographic observations described here show that Mg^{++} administration increases the effect of *ATP* on the conducting system whilst decreasing its effect on the myocardium. Similar effects were observed in experiments on the isolated perfused rabbit's heart. This phenomenon is thought to be due to the interference of Mg^{++} in the enzymic breakdown of *ATP* (Green and Stoner, 1949).

Although *ATP* has such a powerful effect on the conducting system of the heart it would seem that this action can still be antagonized by adrenaline. This action of adrenaline in facilitating conduction through the bundle has been subject to very little experimental investigation in the past largely due to the difficulties of producing graded heart block under experimental conditions. Our observations, therefore, may indicate an approach to this problem.

Quinine, quinidine, and mepacrine also clearly hinder the development of the *ATP* effect but it is not at all clear why they should have this action. Indeed one might have expected *ATP* to have had a greater effect after the administration of these compounds. Our failure to elicit a similar effect with paludrine even when, in animals, very large doses were given, prevents us from agreeing with Raventós (1948), that there is an antagonism between the antimalarial drugs and the cardiac effects of the adenyl derivatives. The antagonism would seem to be between these compounds and certain members of the quinoline and acridine series. The further aspects of this antagonism are dealt with elsewhere (Green and Stoner, 1949). Whilst no explanation of the mechanism involved can yet be given there is no evidence to suggest that it is due to the interference of these quinoline and acridine derivatives in the metabolism of nucleotide.

Summary

The effect of the intravenous injection of adenosine triphosphate (*ATP*) on the electrocardiogram has been studied in human subjects, cats and guinea pigs.

The effect of *ATP* on cardiac rhythm varies with the dose. Whilst very small doses may give sinus tachycardia, the normal effect is to cause sinus slowing, prolongation of the A-V interval and second degree A-V block. Large doses frequently

cause standstill either of the ventricles or the whole heart.

ATP acts mainly on the S–A node in the cat and man but mainly on the A-V node in the guinea pig.

It has been shown that part of the *ATP* effect in the cat and man is mediated through the vagus.

Equimolecular amounts of adenosine will reproduce the effect of *ATP* on cardiac rhythm in the guinea pig and also in the cat if the vagi are first inactivated.

The effects of *ATP* are not confined to cardiac rhythm, and other changes in the electrocardiographic complexes were seen in both man and animals which were thought to be due to a direct action on the myocardium. These changes were not seen after adenosine.

The effect of the previous administration of certain compounds on the response to *ATP* was also observed with the following results.

(1) *Magnesium sulphate* increased the effect on cardiac rhythm and decreased the action on the myocardium.

(2) *Adrenaline* shortened the period of heart block.

(3) *Quinine, quinidine, and mepacrine* all decreased the effect on cardiac rhythm.

(4) *Paludrine* had no significant effect on the response.

ATP administered intravenously for periods up to three months produced no significant improvement in 15 cases of rheumatoid arthritis.

The significance of these observations and their relationship to other of our findings has been discussed.

We wish to thank Professor H. N. Green for his advice and Dr. K. H. Hardy of Wharncliffe E.M.S. Hospital for providing the curves of Case 7.

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FAMILIAL CARDIOMEGALY

BY

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When valvular, hypertensive, and congenital heart disease have been excluded as causes of cardiac enlargement, some rarer condition should be sought, but only after excluding bradycardia, pericardial disease, sternal depression, or an elevated diaphragm, which by themselves without real enlargement produce an exaggerated cardiac silhouette on cardioscopy. Such being eliminated, there remains a group where the cause of cardiac enlargement is obscure, and it is the purpose of this paper to describe cases with common subjective and objective symptoms, and to propose a syndrome that serves to explain a hitherto ambiguous form of cardiac enlargement and facilitates clinical diagnosis of the condition.

Notes of Three Cases in One Family

Case 1. Male, aged 18 years. He was referred by a service medical board which sought an explanation for the displacement of his apex beat. He admitted to no symptoms at the time and he appeared to be a well-developed healthy youth. The pulse was irregular from extrasystoles with brief periods of paroxysmal tachycardia. The blood pressure was 120/80. The apex beat was forcible and was displaced as far as the left anterior axillary line. The heart sounds were clear and there were no murmurs. A triple rhythm was present from the addition of the third heart sound. There was no enlargement of the liver or spleen, and further examination found no abnormal signs elsewhere including the central nervous system. The Wassermann reaction was negative. The blood sugar and cholesterol were both normal, and so was the sugar tolerance test; there was no ketosis. The cardiogram (Fig. 1) showed extrasystoles and exceptionally wide QRS complexes with inverted T waves. On cardioscopy (Fig. 3) there was great enlargement of the heart, and particularly of the left ventricle; the border of which was remarkably quiet compared with the mobile right auricle.

While under observation for two months, the extrasystoles became more frequent and when attacks of paroxysmal tachycardia increased in number and severity, the patient was handicapped in his work at times by giddiness. At last, when tachycardia (Fig. 2) persisted for two days, pulmonary œdema (Fig. 4) developed and he died on the third day.

Summary of Necropsy (*P.M.* 121/1947). By Professor Dorothy Russell of the Bernhard Baron Institute of Pathology.

Acute pulmonary œdema. Heart failure. Familial Cardiomegaly. Clear yellow pericardial effusion (4 oz.). Slight whitish opacity of most of visceral pericardium over both ventricles. Milk-spot (2·5 by 1·2 cm.) on anterior surface of right ventricle. Foramen ovale patent (about 1 cm. diameter), the orifice being valvular. Great thickening (up to 4 cm.) of myocardium of left ventricle, without appreciable dilatation, composed of pale brown moderately firm tissue blotched with numerous ill-defined pale areas of fibrosis (Fig. 5). Similar proportionate thickening of other chambers of heart (Fig. 6), but least marked of left auricle (5 cm. diameter; 0·4 cm. thick). All valves normal apart from congenital fenestration of two pulmonary cusps. Coronary arteries normal and enlarged in proportion to ventricles; no atheroma. Aorta of normal circumference (6 cm. at ring, and 0·2 to 0·25 cm. thick). Very slight atheroma. Early mucinous degeneration of media of aorta found microscopically.

Clear yellow pleural effusions (right, 12 oz.; left, 5 oz.). Almost solid œdema of right lung, showing microscopically variable numbers of red corpuscles and phagocytes in alveolar spaces; purulent bronchitis and early broncho-pneumonia present in a few places. Left lung similar but showing, microscopically, a layer of fibrin coating respiratory bronchioles and some alveoli. Enlargement of gland at tracheal bifurcation, and another above right bronchus, by miliary and larger caseous

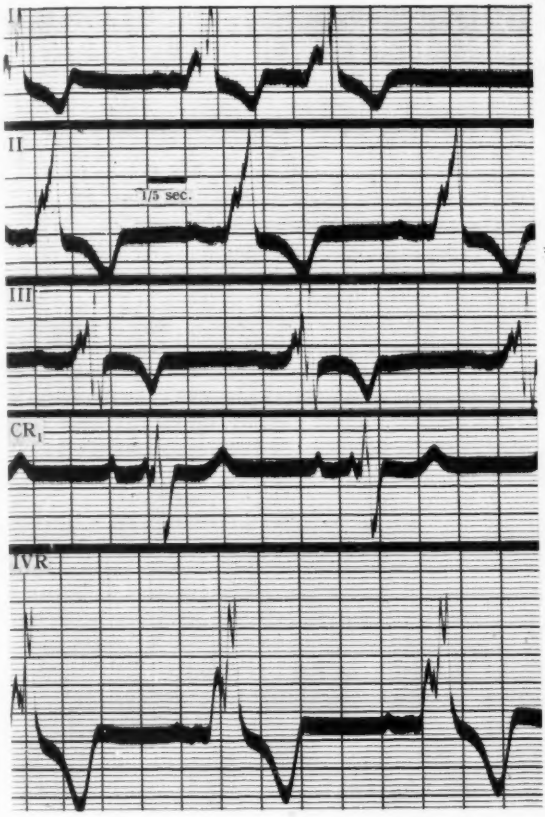

FIG. 1.—Electrocardiogram from Case 1. Sinus rhythm with extrasystoles; exceptionally wide QRS complexes with four R waves showing in IVR, and deep inversion of the T waves in many leads.

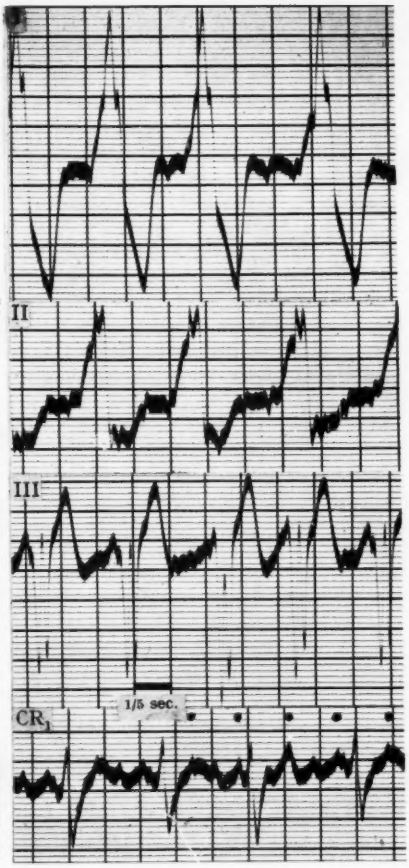

FIG. 2.—Electrocardiogram from Case 1. Paroxysmal tachycardia with a high auricular rate and A-V dissociation.

tubercles, with considerable focal fibrosis. No tuberculosis found in lungs. Central congestion of liver. Chronic congestion and œdema of spleen, showing microscopically two miliary tubercles in pulp. One old infarct in spleen and one in right kidney. Congestion and severe post-mortem degeneration of kidneys. Persistent glandular thymus. No abnormality, macroscopic or microscopic, in endocrine glands. (Only one parathyroid identified.) Post-mortem digestion of stomach. No macroscopic or microscopic abnormality found in brain or spinal cord. Middle ears normal. Cyanosis of extremities. No subcutaneous œdema. A well developed and well nourished young man.

Weights. Body, 62·5 kg. (height, 1·7 m.); heart, 1134 g.; liver, 1921 g.; kidneys, 333 g.; spleen, 333 g.; brain, 1495 g.; suprarenals, 13 g.; thyroid, 56 g.; thymus, 20 g.; testes, 21 g.; pituitary, 0·6 g.

Microscopic examination. Portions of the left ventricle and right auricle were fixed in Bouin's fixative. The rest of the heart was fixed in formaldehyde, blocks being taken on the following day from both ventricles, interventricular septum, and sino-auricular node. In addition to hæmatoxylin and

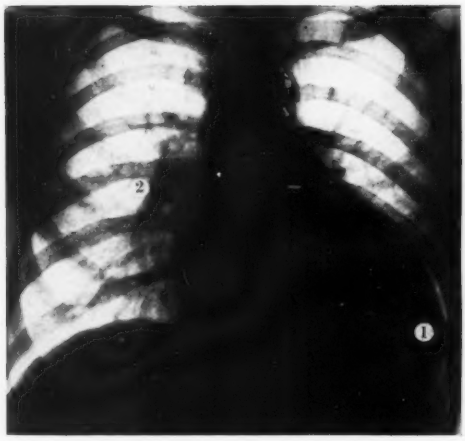

FIG. 3.—Teleradiogram from Case 1. Great enlargement of the heart and especially of the left ventricle (1); much pulmonary congestion (2).

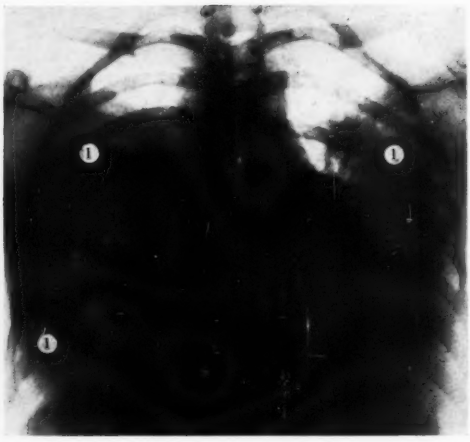

FIG. 4.—Teleradiogram from Case 1. Pulmonary œdema (1) is added to the great cardiac enlargement seen in Fig. 3.

eosin, iron hæmatoxylin and van Gieson and phosphotungstic-acid hæmatoxylin, sections from all blocks were stained by Best's carmine for glycogen. Frozen sections of a piece of left ventricle were stained with Sudan III for fat.

Heart. In all parts examined there is dense patchy fibrosis of the myocardium, especially beneath the endocardium and pericardium, and gross hypertrophy of the muscle fibres (Fig. 7). The hypertrophy often appears greatest where there is most fibrosis. In ordinary stains the fibres are occasionally greatly vacuolated, but vacuolation in general is rather inconspicuous, except in phosphotungstic-acid hæmatoxylin preparations, where high magnifications frequently reveal clusters of small vacuoles in the centres of fibres, or groups of reddish-brown granules in a similar situation. In such fibres the longitudinal fibrils are restricted to the periphery of the muscle cell and cross-striation is lost. Cross-striation is preserved in many fibres devoid of vacuoles and granules. There is no fatty degeneration. The Bouin-fixed sections show conspicuous deposits of glycogen in many scattered fibres in both left ventricle and right auricle. There are no circumscribed areas in which all or most fibres are so affected; the change is diffuse. A good deal of finely granular material stained by Best's carmine is present in the intermuscular connective tissue and in the walls of capillaries. In the formalin-fixed tissue, however, there is little evidence of glycogen. The fibrous tissue in the myocardium contains few spindle cells and occasional small lymphocytes which are mostly perivascular. Occasional larger clumps of small round cells appear to be due to submiliary granulomatous tubercles, one being identified with certainty in the interventricular septum, and one in the pericardium of the left ventricle. The pericardium elsewhere is little affected; there are a few small lymphocytes about the vessels, which are engorged. No changes were found in the special muscle fibres of the conducting system.

Liver. In a block fixed in Bouin's fluid there is great congestion and atrophy of the centres of the lobules; in places adjacent atrophied areas are confluent. There is no fibrosis. A good deal of glycogen is present as fine cytoplasmic granules in the better preserved cells of the periportal parenchyma.

Muscle. Portions of the tongue and vastus externus muscle were fixed in Bouin's fluid. In the tongue glycogen is restricted to the squamous epithelium and some cells of the mucous glands. In the vastus externus large quantities of glycogen are present, some being in the muscle fibres but most has escaped into the interstitial tissue. Patchy vacuolation of the fibres is demonstrated by other stains, but the degree of vacuolation appears trivial in comparison with the amount of glycogen. A special search for glycogen was made in Bouin-fixed material from the kidney, spleen, and central nervous system with negative results.

FIG. 5.—Photogram of the heart in Case 1. There is very great general hypertrophy and especially of the left ventricle (1) which shows grey patches of fibrosis (2).

Case 2. Male, aged 20 years. His appearance was healthy and he complained of no symptoms when he was referred by a service medical board because of great outward displacement of the apex beat. Later, he admitted that during the past six months he had been compelled through giddiness to halt the omnibus he drove, but had never lost consciousness. The pulse was normal in rate and irregular from auricular fibrillation. The blood pressure was 125/80. The apex beat was near the left anterior axillary line and was forcible. The heart sounds were clear and there were no murmurs. Triple heart rhythm was present from addition of the third heart sound. There was no enlargement of the liver, nor of the spleen, and on examination the other systems, including the nervous system, were normal. The blood sugar and the blood cholesterol were both normal. The electrocardiogram showed

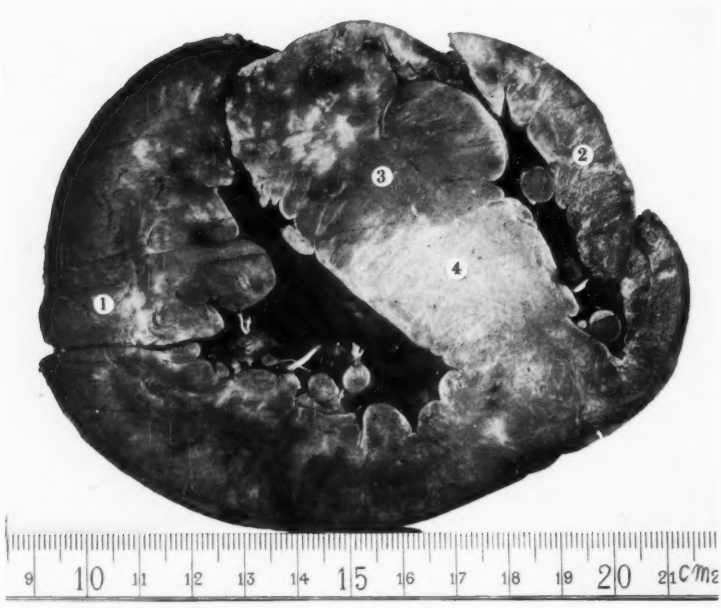

FIG. 6.—Cross-cut of the heart in Case 1 to show great hypertrophy of the left ventricle (1), right ventricle (2), and the septum (3), which shows extensive fibrosis (4).

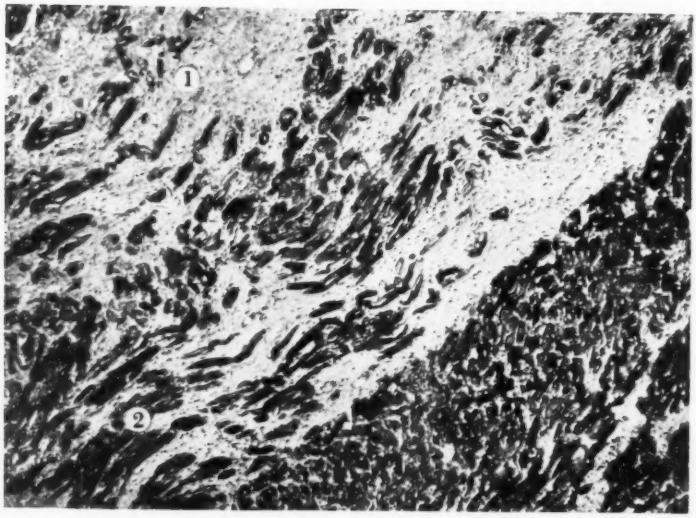

FIG. 7.—Microscopical section of the myocardium from Case 1, showing great fibrosis (1) and hypertrophy of surviving muscle fibres (2).

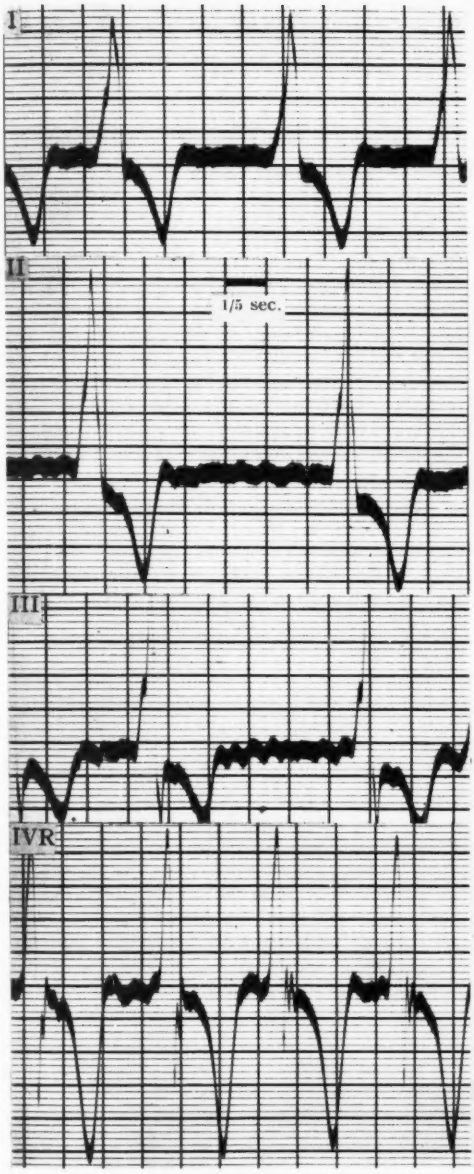

FIG. 8.—Electrocardiogram from Case 2. Auricular fibrillation; wide QRS complexes with deep inversion of the T waves in all leads.

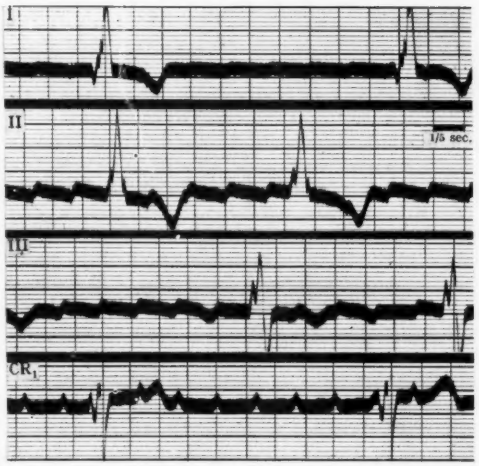

FIG. 9.—Electrocardiogram from Case 2. Auricular flutter with slow ventricular rate. Varying A-V dissociation.

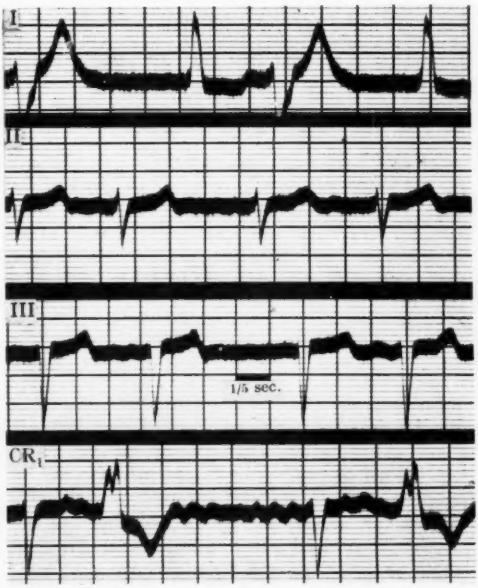

FIG. 10.—Electrocardiogram from Case 3. Auricular fibrillation and extrasystoles; the T wave is inverted in lead I, and the R wave is small in CR1.

auricular fibrillation, exceptionally wide QRS complexes, and deeply inverted T waves (Fig. 8). Another time (Fig. 9) he showed auricular tachycardia with infrequent ventricular rate. On cardioscopy (Fig. 11) there was great enlargement of the heart, and particularly of the left ventricle, the left border of which was remarkably quiet compared with the pulsatile right auricle at the opposite cardiac border.

Case 3. Female, aged 43 years. For 12 years she had suffered from infrequent but severe syncopal attacks. Her pulse was about 70 a minute and was irregular from auricular fibrillation. The blood pressure was 130/90. The apex beat was displaced outwards and was forcible. The heart sounds were clear and there were no murmurs. There was conspicuous splitting of the second heart sound and this was confirmed by the phonocardiogram. There was no enlargement of the liver nor spleen, and examination of other systems showed no abnormal signs. There were extrasystoles and auricular fibrillation with inversion of the T 1 (Fig. 10). On cardioscopy (Fig. 12) there was moderate enlargement of the heart, and especially of the left ventricle.

These three patients illustrate the familial and hereditary nature of the illness; Cases 1 and 2 were brothers and were the sons of Case 3, whose husband and a third son, aged 17 years, were healthy; an infant son had died at the age of 18 months from "heart trouble"; her parents died at the ages of 34 and 35, but the manner of their deaths could not be ascertained; a brother and sister as well as their offspring were healthy; one sister died suddenly in a tramcar at the age of 26 although she was thought to be healthy up to that time; another sister died unexpectedly at the age of 30; a brother while on his way to work one morning dropped dead on the pavement at the age of 21; details of necropsy in these cases cannot be traced, but the manner of their deaths makes it likely that at least six members in two generations of the same family suffered from the condition that is described here (Fig. 13). A family history of the same illness was also obtained from a patient reported at the Massachusetts General Hospital (1942) and also in one described by Addarii and Mahaim (1946).

In addition to the three cases already described there were six others whose symptomatology and clinical signs were so similar as to make me believe that they suffered from the same condition. In one where a necropsy was carried out, fibrosis of the myocardium was found to be the underlying lesion as in Case 1, but no family history of the condition could be obtained from any of the six cases, although in none had it been possible to examine other members of the family.

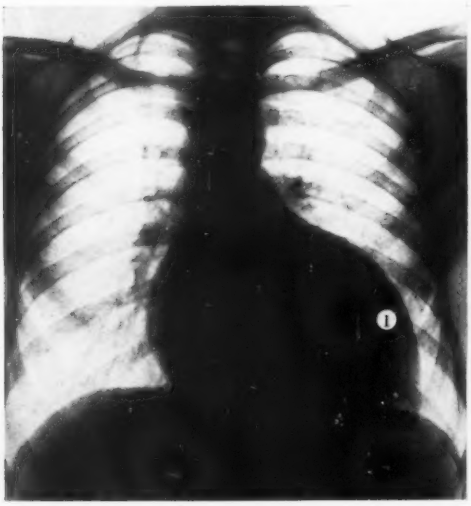

FIG. 11.—Teleradiogram from Case 2 showing great general enlargement of the heart and especially of the left ventricle (1).

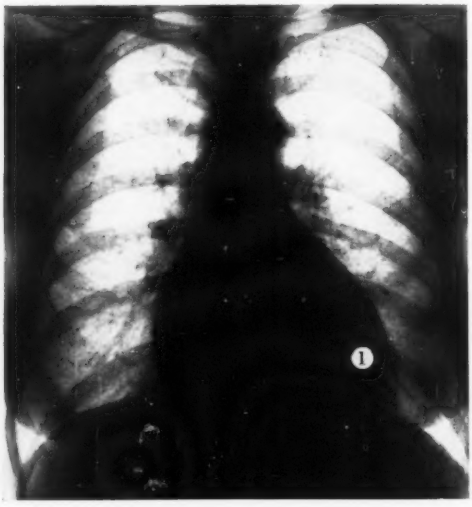

FIG. 12.—Teleradiogram from Case 3 showing moderate general enlargement of the heart, and especially of the left ventricle (1).

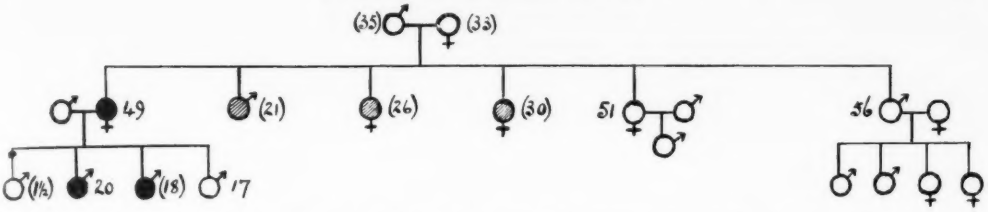

FIG. 13.—Scheme identifying patients affected with Familial Cardiomegaly in one family. The black symbols represent members suffering from familial cardiomegaly; the shaded symbols indicate members probably affected by the same illness; the unshaded symbols are unaffected members. The numerals are the ages in years, and when bracketed they indicate the age at death.

OTHER CASE NOTES

Case 4. Male, aged 35 years. Two years before he was rejected for military service by a medical board which advised him not to do any heavy work. He remained well until a month before when he fainted in a chair and afterwards discovered a lump on the back of his head which he supposed had resulted from his head falling backward on to the chair. Thereafter he experienced spells of giddiness which made him uncertain of himself when walking, but when they passed he would feel quite well. Only once did he lose consciousness. No other members of the family were similarly affected.

His appearance was healthy. The pulse was slow (52 a minute), and was irregular from extrasystoles, which disappeared for a short time after exercise. The blood pressure was 115/70. The apex beat reached the anterior axillary line and was forcible in character with a double impulse. There was no thrill. A triple heart rhythm was present from the addition of the third heart sound and this was confirmed by the phonocardiograph. There were no murmurs. Further routine clinical examination showed no abnormal signs in other systems. The electrocardiogram (Fig. 14) showed bradycardia, bundle branch block, and extrasystoles. On cardioscopy (Fig. 16) there was great generalized enlargement of the heart. The Wassermann reaction was negative. He continued with his work, but complained of giddiness on occasions. Three years later there was another syncopal attack, but he recovered only to fall dead as he was walking home from work. There was no necropsy.

FIG. 14.—Electrocardiogram from Case 4. Sinus bradycardia with extrasystoles; wide QRS complexes; prominent Q, R–T deviation, and inversion of the T wave in lead I; Q wave, and R–T deviation in IVR.

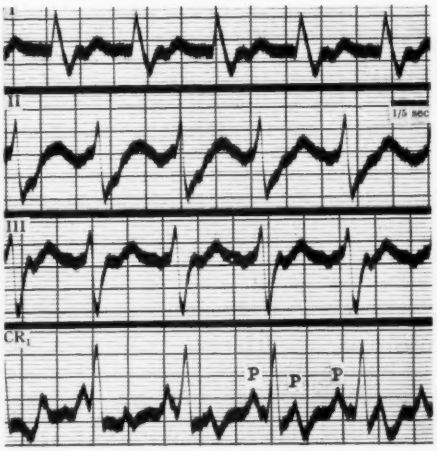

FIG. 15.—Electrocardiogram from Case 5 during an attack of paroxysmal tachycardia with 2 to 1 A-V dissociation which is best seen in CR1.

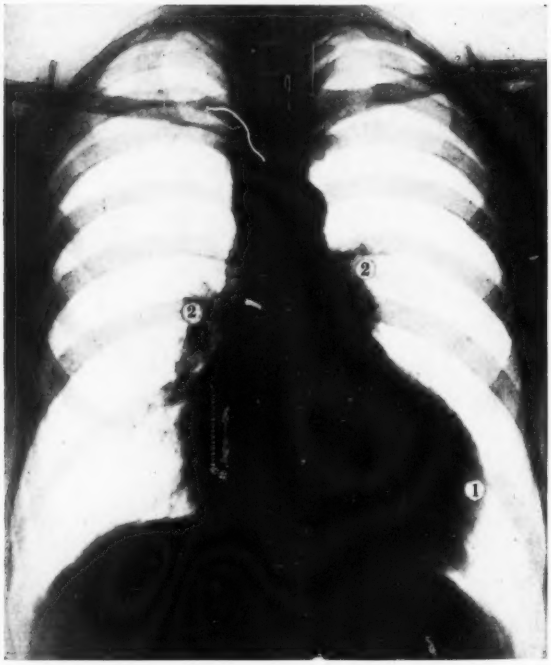

FIG. 16.—Teleradiogram from Case 4. Great enlargement of the heart and especially of the left ventricle (1); pulmonary congestion (2).

Case 5. woman, aged 63 years. Three years before, she complained of dizziness and at times lost consciousness. Later, palpitation became troublesome and she said that the heart occasionally beat very rapidly. The pulse was 56 and irregular from extrasystoles, and she was sometimes found with paroxysmal tachycardia. There was no hypertension. The apex beat was displaced outwards as far as the anterior axillary line and it was diffuse and forcible. There was an obvious triple heart rhythm from addition of the third heart sound. A systolic murmur in the mitral area occupied mid-systole and there were no diastolic murmurs. Although the thyroid was enlarged, there were no signs of thyroid toxæmia. There were no abnormal signs in any other system. At one time sinus bradycardia with ventricular complexes of bundle branch block, and at other times paroxysmal tachycardia with 2 to 1 (Fig. 15) or a higher grade A-V dissociation, were seen. On cardioscopy (Fig. 17) there was great enlargement of the heart, particularly of the right side. She is still alive.

Case 6. Woman, aged 62 years. She was admitted to hospital for attacks of palpitation 15 years ago; although the arrhythmia did not recur in hospital, radiological examination showed enlargement of the heart. Throughout the years she continued to experience these attacks and in two of them she lost consciousness. Two years ago an electrocardiogram showed sinus bradycardia and bundle branch block. Twelve months ago a cardiogram during the attack showed auricular fibrillation and she again reverted to normal rhythm. There were more episodes of paroxysmal auricular fibrillation, and unconsciousness once from cerebral embolism. She gradually recovered from the paralysis and for three months she had not experienced any palpitation while the heart rhythm continued as auricular fibrillation with infrequent ventricular rate. The cardiogram showed right bundle branch block in addition to fibrillation. The blood pressure was normal. The apex beat was out a little way and there was moderate cardiac enlargement. No triple heart rhythm was present at the single clinical examination. There was no enlargement of the liver or spleen and the urine was clear. Since the auricular fibrillation became established the syncopal attacks had become less frequent.

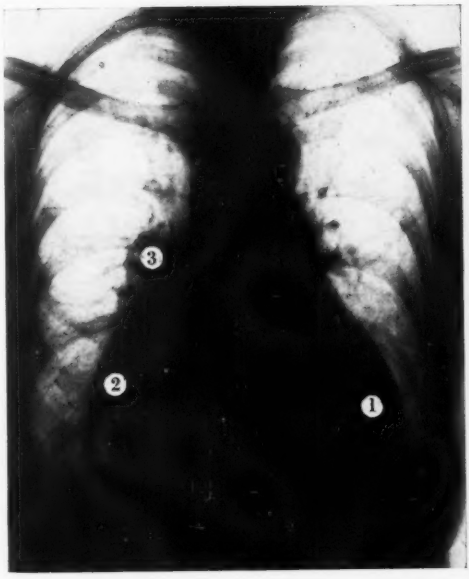

FIG. 17.—Teleradiogram from Case 5. There is enlargement of the left ventricle (1) and especially of the right auricle (2). Pulmonary congestion (3).

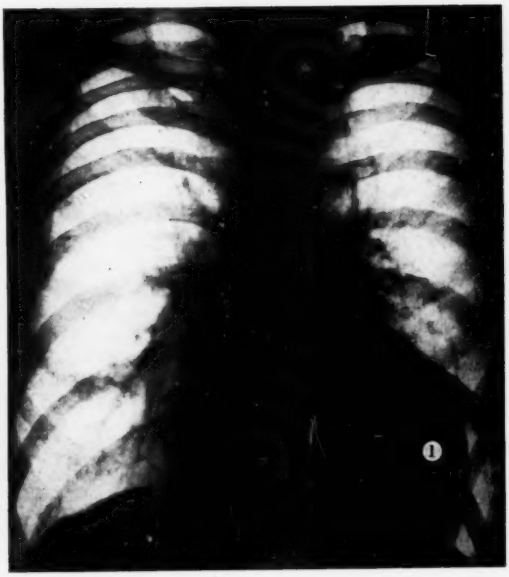

FIG. 18.—Teleradiogram from Case 7, showing enlargement of the heart and especially of the left ventricle (1).

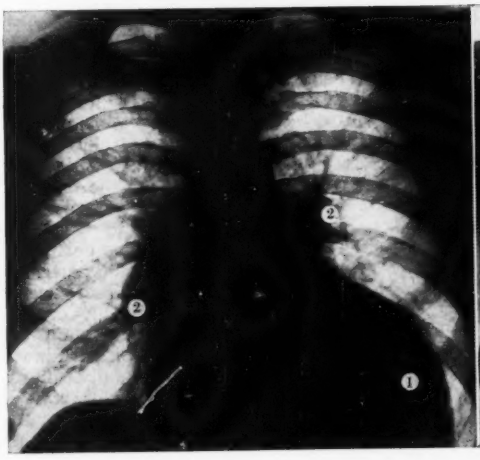

FIG. 19.—Teleradiogram from Case 9, showing great enlargement of the heart and especially of the left ventricle (1) with pulmonary congestion (2).

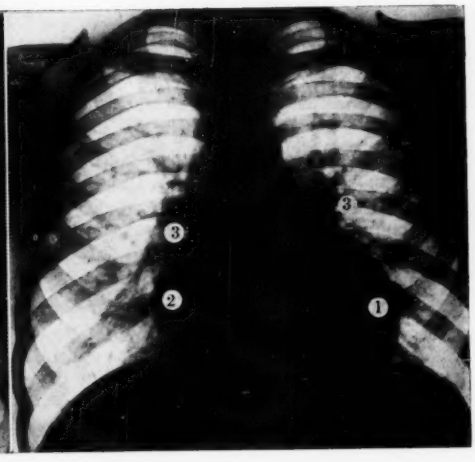

FIG. 20.—Teleradiogram from Case 8 showing generalized enlargement of the heart and especially of the left ventricle (1) and right auricle (2), as well as pulmonary congestion (3).

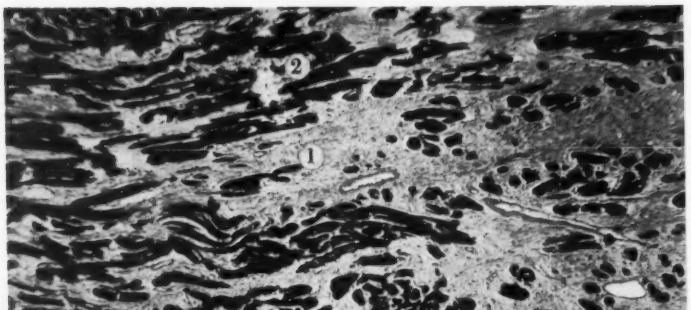

FIG. 21.—Microscopical section of the myocardium from Case 8 showing great fibrosis (1) and hypertrophy of surviving muscle fibres (2).

Case 7. Man, aged 41 years. Although he had complained of breathlessness on exertion for some years he had not sought medical advice, and enlargement of the heart was discovered on routine mass radiography. He had neither palpitation nor giddiness. No other members of the family complained of heart trouble, but none of them was examined.

The pulse was regular and 76 a minute. The blood pressure was 120/85. The apex beat was in the left anterior axillary line. A systolic murmur was heard in late systole in the mitral area and there was prominent splitting of the second heart sound which was confirmed in the phonocardiogram. There were no diastolic murmurs.

There was no enlargement of the liver and no other abnormal physical signs. The urine was clear. The electrocardiogram showed bundle branch block. On cardioscopy (Fig. 18) there was considerable enlargement of the heart especially involving the left ventricle; there was no pulmonary congestion.

Case 8. Boy, aged 12 years. His mother said that for several months he had been subject to attacks of fainting. Three such attacks occurred in the previous fortnight. They had all taken place while he was at school. There was never any warning and he would fall down suddenly. In one attack he hurt his head badly when it banged against the floor. There were no other complaints, and the mother had been told he had epilepsy. There was no family history of a similar illness.

The boy looked healthy. The pulse was rather slow (60 a minute) and was regular. The blood pressure was low (105/50). The apex beat was out a little way and he showed a short soft systolic murmur. There was triple heart rhythm. No other physical signs presented and there was no enlargement of the liver or spleen. The urine was clear. The cardiogram (Fig. 22) showed sinus rhythm at a slow rate (48 a minute) and a very high voltage. The P–R period was not prolonged nor was the QRS period. There was deviation of the R–T segments, and the T waves were diphasic in certain leads. On cardioscopy (Fig. 20) there was generalized enlargement of the heart and especially of the left ventricle.

He continued to suffer from epileptiform attacks. Four years later, at the age of 16, he developed acute appendicitis and recovered uneventfully from the operation. The day following his discharge from hospital while walking home from the cinema he was seized with severe breathlessness and died on his way to hospital.

At necropsy there was considerable enlargement of the heart (weight not recorded), and particularly of the base of the left ventricle. There was no embolism and no abnormality of the coronary circulation. On microscopical examination there was great hypertrophy of the myocardial fibres of the left ventricle with much interstitial fibrosis (Fig. 21). (See appendix for mother's history.)

Case 9. Man, aged 33 years. He was without symptoms apart from palpitation until three months before when he began to get breathless on exertion. His voice had altered and this brought him to hospital where palsy of the left recurrent laryngeal nerve was found. The pulse was irregular from

extrasystoles and the nature of the arrhythmia was confirmed by the cardiogram (Fig. 23) which also showed wide QRS complexes like those of bundle branch block. The apex beat was displaced outwards as far as the left anterior axillary line and radiological examination confirmed the presence of great enlargement of the heart (Fig. 19). The blood pressure was 120/75. The first heart sound showed splitting and there was a slight systolic murmur in the mitral area. The house physician did not note that any triple heart rhythm was present. There were no other abnormal signs. The urine was clear. The sugar tolerance test was normal and the Wassermann reaction was negative. He left hospital without a definite diagnosis having been made. He died a few months later but there was no necropsy.

Discussion

Unexplained cardiac enlargement is not common. Now and again, however, there comes for diagnosis a patient in whom the cause of an enlarged heart is not obvious. In older patients hypertension may explain cardiac hypertrophy, even though the blood pressure at the time is normal, perhaps reduced by cardiac infarction which can by itself cause a moderate or greater degree of cardiac enlargement. In a younger patient such diagnosis will seldom apply. Bradycardia, with or without heart block, will explain some instances of enlargement of the cardiac silhouette found on radiological examination. An unusual condition like amyloidosis of the heart has been the cause of moderate enlargement in rare cases. Enlargement of the heart from glycogenic disease is even a rarer event in adults. Whenever a single example of unexplained enlargement of the heart is seen the need to find the precise cause has not appeared so important, but when two

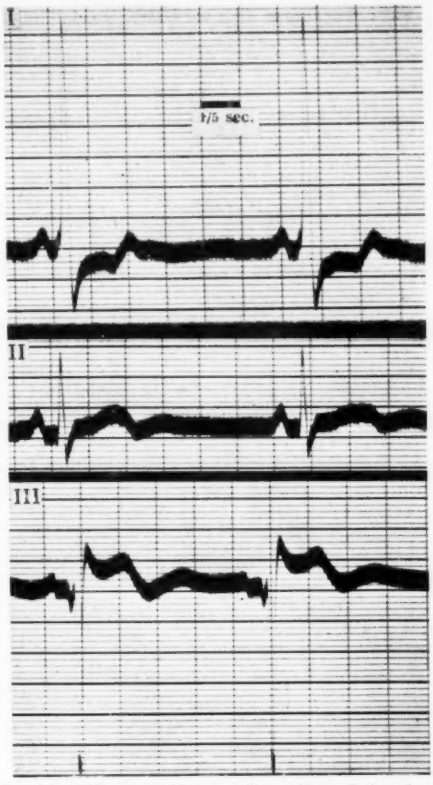

Fig. 22.—Electrocardiogram from Case 8 showing sinus bradycardia, deviation of the R–T segments and diphasic T waves.

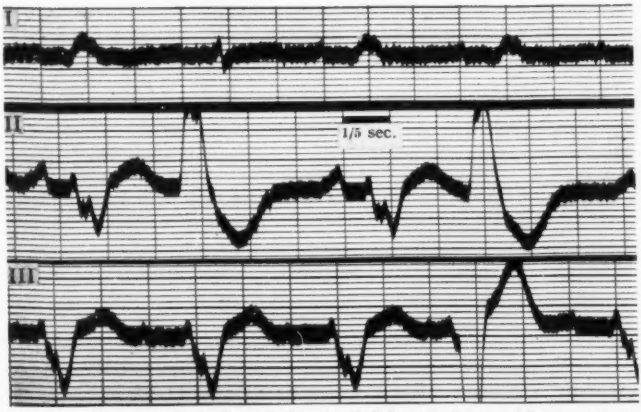

Fig. 23.—Electrocardiogram from Case 9 showing left bundle branch block and extrasystoles.

or more such cases appear, a search for a common aetiology becomes more vital.

When the pathological findings have not been available or are equivocal in these odd instances of cardiac enlargement they have been described under such titles as 'idiopathic enlargement,' or 'unexplained enlargement of the heart in young subjects' (Whittle, 1929; Kugal and Stoloff, 1933; Levy and Rousselot, 1933; Mahon, 1939; Levy and von Glahn, 1937; Case Records of Massachusetts General Hospital, 1942; Norris and Pote, 1946; and Vulliamy, 1947). When inflammatory changes or fibrosis of the myocardium has been an obvious finding at necropsy, they have appeared as acute non-specific myocarditis (Helwig and Wilhelmy, 1939; Candel and Wheelock, 1945), myocardial fibrosis in young men (Sellars and Phillips, 1946), and chronic fibroblastic myocarditis (Ware and Chapman, 1947). Again, the pronounced degree of cardiac enlargement has sometimes been emphasized in a title such as massive cardiac hypertrophy (Doane and Skversky, 1944), while the arrhythmia which is common in such conditions has twice furnished the heading (Major and Wahl, 1932; Addarii, Mahaim, and Winston, 1946). Few of the cases published under these several titles are instances of the condition described here.

In the published cases of obscure cardiac enlargement the metabolism of glycogen has often been discussed. In Case 1 of the present series, deposits of glycogen appeared in many scattered muscle fibres in the left ventricle and the right auricle, and in the vastus externus muscle. Russell (1948) sought to control this finding from the examination of 11 cases at necropsy which took place from 4 to 34 hours after death; they showed scanty amounts of glycogen in the ordinary muscle fibres compared with that found in Case 1 which was examined 56 hours after death. Berlinger (1912) found little glycogen in 25 hearts beyond occasional traces in those cases where necropsy was delayed till five hours after death; the auricular appendage contained more glycogen than other parts. The work of Vallance-Owen (1948), however, has shown that post-mortem material does not appreciably lose its glycogen content up to 50 hours before fixation if kept in a cold chamber; this has corrected the customary belief that when glycogen is found in old post-mortem tissue, more would have been found had fixation of the tissue been carried out immediately after death. The small amount of glycogen found in the liver in Case 1 is without significance for Popper and Wozasak (1930) found glycogen in cases of heart failure. No glycogen was found in the kidney, spleen, or central nervous system in Case 1. The patients described in this paper are not examples of glycogenic or von Gierke's disease (1929), a condition found in infants where glycogen accumulating in the liver, and rarely in the kidneys and the heart, causes the viscus to enlarge, and where biochemical tests establish a failure in glycogenolysis so that there is ketosis, hypoglycæmia, with absence of the normal rise in the blood sugar after adrenaline, and an abnormal blood sugar curve after glucose, together with a raised blood glycogen and blood cholesterol (Ellis and Payne, 1936). Gardner and Simpson (1938) found 40 reported cases of glycogenic disease, but in none of them had death taken place suddenly or required a medico-legal examination. They recorded the first example of this, a boy aged 11 years. The age of this patient was also exceptional because in the ten previously recorded cases of glycogenic disease in which the presence of excessive glycogen had been demonstrated in the heart muscle, either by Best's stain or by chemical analysis, the ages ranged from 5 weeks to 8 months. Mason and Anderson (1941) have recommended that the term von Gierke's disease should be confined to cases in which there is failure of glycogenolysis. I agree with this view and would add a second criterion, namely, that the designation should be applied to the heart only when it has enlarged from accumulation of glycogen within it. If these rules are applied it is likely that the diagnosis needs to be considered in infants and only rarely in older children or adults.

Of greater significance is the similarity of the signs met with in the present series to those found in Friedreich disease. The familial and hereditary nature of the illness in 3 out of 9 cases is comparable with a series of patients with Friedreich disease where 18 of 38 were the only members of their family to be affected. The heart is commonly affected in Friedreich disease for 12 out of 38 patients showed prominent electrocardiographic changes (Evans and Wright, 1942); such irregularities in the cardiogram told of an interruption of the conducting tissue with complete and bundle branch block, or of involvement of the myocardium producing inversion of the T waves reminiscent of cardiac infarction. Because of the lesser degree of myocardial fibrosis in Friedreich disease, the remarkable widening of the QRS complexes in some of the cases described in this paper, is not found. The size of the heart is not as great in Friedreich disease, but to this finding there are exceptions especially when heart block is present. On pathological grounds too the similarity of Friedreich disease to the condition dealt with here is arresting. Russell (1946), reporting specially on the heart in four cases of Friedreich

disease, found a piece-meal destruction of muscle fibres with fibrosis and hypertrophy of the surviving fibres, and remarkably little cellular inflammatory infiltration; there was no glycogen in one heart, but it was not sought specially in the other three. Naturally, the relation of this condition to Friedreich disease would be more definitely established if instances of each were met with in one family, but such a coincidence has not so far come to my notice.

Summary

There is described in this paper a distinct syndrome having a definite clinical, cardiographic, and pathological pattern.

Clinically it is characterized by light symptoms at the start, and is often found fortuitously in a young adult during routine examination preliminary to admission to military service or civilian occupation. Ultimately, palpitation, momentary giddiness, and frank Stokes-Adams attacks may develop, and death may come suddenly during such episodes, or as the result of heart failure precipitated by the onset of paroxysmal tachycardia.

On examination the pulse is usually irregular from extrasystoles, paroxysmal tachycardia, auricular fibrillation, or heart block. There is great enlargement of the heart, and the blood pressure is normal. The heart sounds are usually clear, and there is either splitting of the second sound, or triple heart rhythm from the addition of the third heart sound. There is no enlargement of the viscera, and serological tests and the blood chemistry are normal.

The *electrocardiogram* shows extrasystoles, paroxysmal tachycardia, auricular fibrillation, or heart block, according to the kind of arrhythmia prevailing at the time; the QRS complexes are usually exceptionally wide, depending on the extent of the fibrosis and the size of the heart, and the T waves are inverted.

On *cardioscopy* there is enlargement of the heart, and as a rule the cardiomegaly is considerable.

The *prognosis* depends on the extent of the fibrosis and the associated cardiac enlargement. Thus, it is poor in young subjects with great enlargement of the heart, but in older subjects with moderate cardiac enlargement the outlook can be favourable although recurrent Stokes-Adams attacks are a handicap if frequent.

Pathologically the condition shows fibrosis of the myocardium is usually conspicuous; this is associated with hypertrophy of the remaining muscle fibres producing great cardiac enlargement. Intracardiac thrombosis initiating embolism is an expected complication. Although glycogen may be present and even in slight excess of the normal, the syndrome described here should be regarded as a separate entity from glycogenic or von Gierke's disease—is usually confined to young children or infants—where a viscus becomes distended by the large accumulation of glycogen within it, and where laboratory tests during life show faulty glycogenolysis. Neither does the syndrome include those cases of hypertrophy of muscle fibres in the absence of myocardial fibrosis.

The *ætiology* of the condition, although obscure, probably rests with an unknown factor which in Friedreich disease involves the central nervous system alone or along with the heart, and in the condition described here affects the heart exclusively, causing myocardial fibrosis. Like Friedreich disease too the condition may be familial and hereditary, or it may arise sporadically and *de novo*.

Having regard to the specificity of the condition and its chief characteristics I propose to name it *Familial Cardiomegaly*.

Appendix

Since this paper was written the mother of Case 8 has been admitted to hospital. She is 42 years of age and for two months has experienced short attacks of paroxysmal tachycardia. Once she lost consciousness for six minutes. Her pulse is regular and the blood pressure normal. The apex beat is in the left anterior axillary line. There are no murmurs. A triple heart rhythm from addition of the fourth heart sound is caused by delayed A-V conduction and there is splitting of the second sound in the mitral area from bundle branch block; these findings have been confirmed by the phonocardiograph. The electrocardiogram shows a prolonged P–R period and bundle branch block. On cardioscopy there is considerable generalized enlargement of the heart and much pulmonary congestion. She is, therefore, another example of familial cardiomegaly, her son, Case 8, having died suddenly at the age of 16 from the same condition. The addition of this patient to Cases 1, 2, 3, and 8 supplies five instances of the disease where a family history of the complaint was present.

I wish to thank Professor Dorothy Russell, not only for reporting on the pathological findings in Case 1, but also for her helpful discussion of the significance of these findings.

Sir John Parkinson, Physician to the Cardiac Department, has given me advice on the writing of this paper. Dr. Maxwell Chance referred Case 1 to me and in this way enabled me to examine a brother (Case 2) and his mother (Case 3). Dr. Francis Camps supplied me with the details of necropsy in Case 8.

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THE EFFECT OF DIGITALIS ON THE VENOUS PRESSURE

BY

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The action of digitalis on the circulation in man is not yet clearly understood. There can be no doubt that it benefits most patients with congestive heart failure, but beyond this there is no certainty.

McKenzie (1905) believed that its value was greatest in cases of congestive heart failure with auricular fibrillation and could then be attributed to slowing of the ventricular rate; Lewis (1937) agreed, maintaining that improvement was infrequent in patients with normal rhythm, because slowing of the heart rate was often inconspicuous. Dock and Tainter (1930) and Katz *et al.* (1938) suggested that digitalis might act primarily by constricting the hepatic vein, a throttle mechanism that was demonstrated in anæsthetized dogs; they claimed that the venous pressure was lowered by means of a bloodless venesection, blood being dammed back in the liver and portal system. Such a theory harmonized with other findings, e.g. digitalis reduced the cardiac output of normal dogs (Harrison and Leonard, 1926) and decreased the size of the heart in normal human beings (Stewart *et al.*, 1938). In 1940, however, one of us was able to show that digitalis lowered the venous pressure in 90 per cent of cases of heart failure with normal rhythm, and that this was due neither to slowing of the heart rate nor to any hepatic vein throttle mechanism; for the venous pressure fell as sharply when cardiac slowing was prevented, and the liver and spleen shrank simultaneously (Wood, 1940). More recently, McMichael and Sharpey-Schafer (1944) showed that mechanical lowering of the right auricular pressure by means of cuffs on the thighs produced effects on the cardiac output in man similar to those resulting from digitalis: in cases of congestive heart failure the right auricular pressure fell and the cardiac output rose; in normal subjects the right auricular pressure fell and the cardiac output fell. They suggested that digitalis might have a primary action in lowering venous pressure to which the other effects were subsidiary. The authors admitted that the venous pressure was lowered but slightly in normal subjects, and conspicuously only when the initial level was high; but they attributed this to a logarithmic effect.

The object of the present investigation was to discover what action digitalis might have on the venous pressure when it was elevated from causes other than congestive heart failure.

Method Used

A consecutive series of twelve cases, in which the jugular venous pressure was raised clinically without any real evidence of congestive heart failure, was studied. The nature of the material is shown in Table I. The raised venous pressure was attributed to a hyperkinetic circulatory state in the cases of anæmia and thyrotoxicosis, and to an increased blood volume in the cases of acute nephritis and artificial hydræmia. Hydræmia was induced by means of sodium chloride 10 g., water 10–12 pints, and D.O.C.A. (desoxy-cortico-sterone acetate) 25–50 mg. daily for 7 to 14 days.

All observations were made with the subject lying more or less horizontal, the head being supported on one or two pillows. The antecubital venous pressure was measured directly as described in a previous paper (Wood, 1940). The right auricular pressure was measured by means of a No. 8, 9, or 10 nylon cardiac catheter and a saline manometer, as described by McMichael and Sharpey-Schafer (1944); only mean pressures can be recorded by this method. The cardiac output was estimated by means of Fick's formula, the arteriovenous oxygen difference being obtained by analysing arterial and right auricular blood samples in a modified Haldane blood gas apparatus, and the oxygen consumption

TABLE I

Case	Condition	Right ventricular pressure, cm. saline above sternal angle at 5–10°	Oxygen consumption, ml. a minute	Oxygen capacity, ml. a litre	Arterio-venous oxygen difference, ml. a litre	Right auricular pressure (or antecubital venous pressure *). cm. saline above sternal angle at 5–10°		Cardiac output, litres/minute		Blood pressure		Pulse rate	
						Before dig.	After dig.	Before dig.	After dig.	Before dig.	After dig.	Before dig.	After dig.
1	Pernicious anæmia ..	—	—	—	—	8·5*	8·5*	—	—	—	—	—	—
2	Pernicious anæmia ..	24	382	48	28·6–37·6	1·5	1·0	10·5	10·0	132/60	140/60	112	108
3	Pernicious anæmia ..	13·5	262	88·5	34–32	−4·5	−4·5	7·4	8·2	120/66	128/66	94	90
4	Thyrotoxicosis and hypochromic anæmia ..	37	380	115	31–39	5·5	5·5	12·6	8·0	205/100	205/100	130	102
5	Thyrotoxicosis and aortic incompetence ..	—	—	—	—	−0·5	±0	9·7	—	120/40	—	90	—
6	Acute nephritis	20	257	169	46·5–51·5	7·5	7·0	5·6	5·6	138/78	165/80	65	58
7	Acute episode in chronic nephritis	15	—	—	59–61	2·5	2·5	—	—	175/115	210/125	70	70
8	? Acute nephritis ..	11	186	169	45–42·5	4·0	4·0	4·1	4·4	130/80	155/85	72	48
9	Artificial hydræmia ..	—	—	—	—	16·0*	16·0*	—	—	—	—	—	—
10	Artificial hydræmia ..	14	208	161	105–115	−2·0	−0·5	1·95	1·8	100/60	110/64	84	76–80
11	Artificial hydræmia ..	—	260	Assumed normal	41–40	−1·0	−2·0	6·4	6·5	160/100	170/100	96	96
12	Chronic constrictive pericarditis	10·5	286	Assumed normal	48–53	4·5	4·5	5·6	5·5	115/70	125/85	80	68–76

by means of a Benedict-Roth spirometer. In some cases the arterial blood was assumed to be 95 per cent saturated with oxygen. The oxygen capacity was either estimated directly by the ferricyanide method or calculated from the hæmoglobin value, results approximating closely when both methods were employed. The catheter was passed without X-ray control: to make certain the tip was in the right auricle, the right ventricle was always entered, and the catheter was then withdrawn slowly until the pressure suddenly fell and conspicuous pulsation ceased.

Results

Congestive Heart Failure. In four controls with clinical congestive heart failure, mostly hypertensives, the venous or right auricular pressure fell sharply and considerably within half an hour of giving 1·5 mg. of digoxin intravenously, whether initial readings were high or relatively low (Fig. 1). At the same time the cardiac output rose, the pulse usually slowed, and the blood pressure rose (Fig. 2). These cases illustrated the well-known response of heart failure to digitalis and proved that the digoxin was potent and that the dose of 1·5 mg. was sufficient.

Anæmia. There were three cases of severe pernicious anæmia: in all the jugular venous pressures were raised as judged clinically. The cardiac output was 10–14 litres a minute in one of them, 7 litres a minute in another, and was not measured in the third. Intravenous digoxin had no effect on the venous or right auricular pressures and did not alter the cardiac output; the blood pressure, however, rose (Fig. 3).

Thyrotoxicosis. There were two cases of thyrotoxicosis in which the jugular venous pressures were raised as judged clinically: one was complicated by moderate hypochromic anæmia, the other by atherosclerotic aortic incompetence. The cardiac output was 12 litres a minute in the first, 9·6 in the second. Intravenous digoxin had no effect on the right auricular pressure in either; the cardiac output fell appreciably in one of them, but this could be attributed to slowing of the pulse rate (Fig. 4).

Acute Nephritis. There was one case of classical acute nephritis, one of chronic nephritis with an acute flare-up, and one in which the diagnosis was

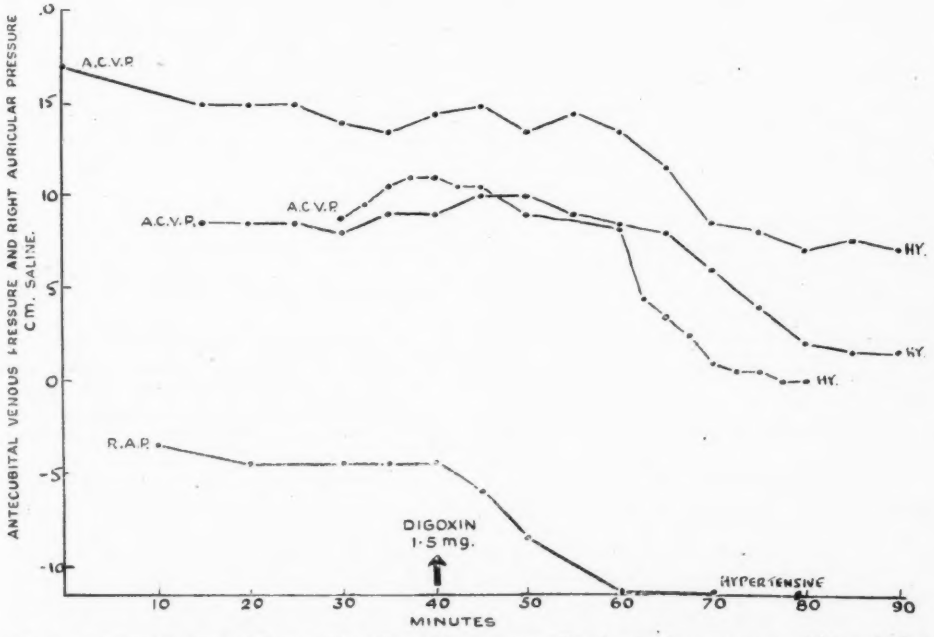

FIG. 1.—Congestive heart failure. The effect of intravenous digoxin on the venous or right auricular pressure in four cases of congestive heart failure with normal rhythm.

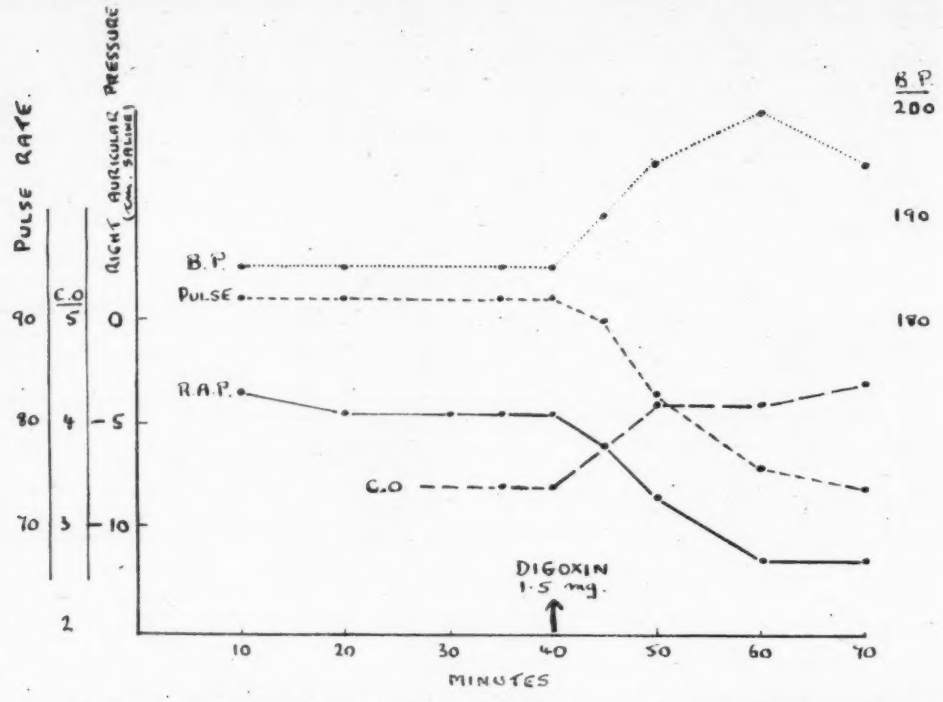

FIG. 2.—Hypertensive heart failure. The effects of intravenous digoxin on the blood pressure, pulse rate, right auricular pressure and cardiac output in a case of hypertensive heart failure. Oxygen capacity and hæmoglobin assumed normal. Oxygen consumption assumed 300 ml./min. A-V difference 87–68 ml./litre. Right ventricular pressure+26 cm. saline. After rest, low sodium and mersalyl for 14 days.

uncertain; this was a case in which transient œdema suddenly developed a fortnight or so after an acute upper respiratory tract infection, but the blood pressure, urine, and measured renal function remained normal. All three had a raised jugular venous pressure.

Intravenous digoxin (1·5 mg.) did not influence the right auricular pressure or cardiac output in any of them; but the blood pressure rose as usual, and the pulse rate tended to fall (Fig. 5).

Artificial Hydræmia. Considerable increase in body weight, generalized œdema, and a raised jugular venous pressure were produced in three cases by means of salt, water, and desoxy-corticosterone. Intravenous digoxin (1·5 mg.) did not effect the right auricular pressure or the cardiac output in two of them, nor the venous pressure in the third (which was not catheterized). The blood pressure rose and the pulse rate fell slightly in the case illustrated (Fig. 6, see p. 90).

Chronic Constrictive Pericarditis. Only one case of Pick's disease was investigated, and the opportunity to catheterize a case of pericardial effusion did not arise. Intravenous digoxin (1·5 mg.) caused a rise in blood pressure and a fall in pulse rate, but had no influence on the right auricular pressure. The cardiac output was not measured when the pulse reached its lowest level, but was not altered 10 and 40 minutes after the injection when the pulse rate was still unchanged or had practically regained its former level respectively (Fig. 7, see p. 91).

SUMMARY OF RESULTS

Digoxin thus had no effect on the right auricular pressure in these twelve cases (Fig. 8). The blood

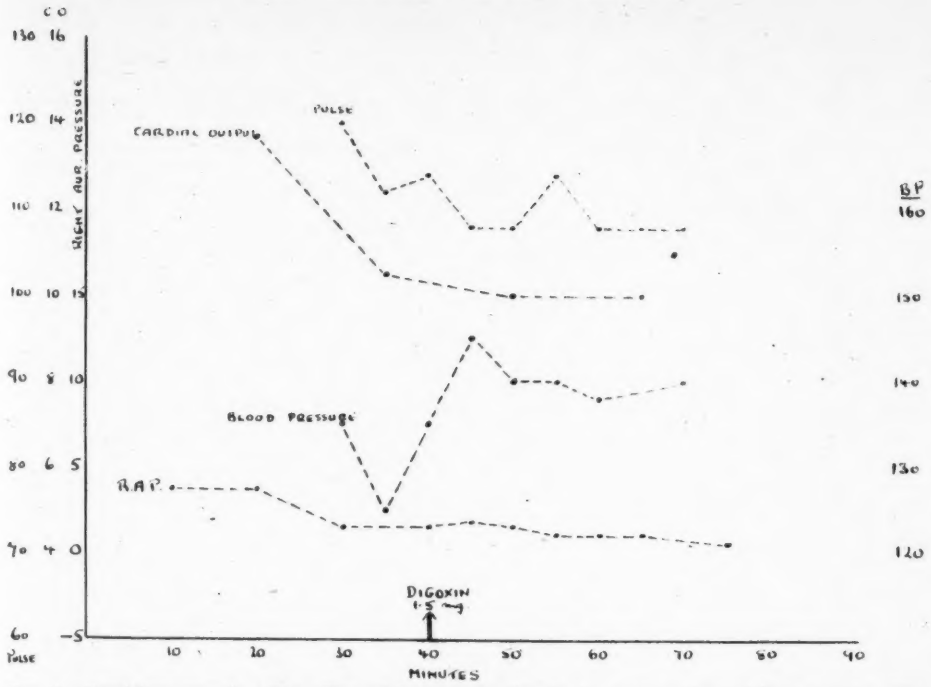

FIG. 3.—Pernicious anæmia. The effect of intravenous digoxin in a case of pernicious anæmia. The cardiac output has fallen with the pulse rate, but there is no effect on the right auricular pressure. Oxygen capacity 4·8 vol. per cent. Hæmoglobin 3·6 g. per 100 ml. (21 per cent Sahli). Early oxygen consumption 390, late oxygen consumption 374. R.V.P. 24 cm. saline A-V difference 28·6–37·6 ml./litre.

pressure usually rose, and the pulse rate tended to fall; the cardiac output also fell if the pulse rate diminished sufficiently.

The cases were selected at random and represented any condition that was encountered by the authors during 1947 and 1948 in which a raised jugular venous pressure could be attributed to causes other than congestive heart failure; moreover, they were consecutive, and no such cases have been excluded.

Absence of congestive heart failure was confirmed by the behaviour of the cardiac output and by the arteriovenous oxygen difference. The former was high or normal, except in one (Case 10) complicated by nausea and vomiting; it fell with rest and slowing of the pulse, and was certainly capable of being raised considerably in some cases, if not in all. The latter was normal or less than normal, and was never increased (except in Case 10). In congestive heart failure proper the cardiac output is low, or if it is normal or raised it is not as high as it should be; in other words the circulation is incapable of meeting the demands of the body, the most consistent finding being an increased arteriovenous oxygen difference (Stead, Warren, and Brannon, 1948).

If digitalis had a primary action in lowering venous pressure it is difficult to believe that it would only influence the right auricular pressure in cases of congestive heart failure. The dose used, 1·5 mg. of digoxin intravenously, was the same as that employed by McMichael and Sharpey-Schafer (1944), was sufficient to raise the blood pressure and slow the pulse rate in most cases, and had the usual effect in heart failure. Nevertheless, it is admitted that a larger dose might possibly be required in the type of cases investigated in this paper.

If digitalis does not have a primary action in lowering venous pressure, its apparent ill effect in cases of chronic pulmonary heart failure secondary to emphysema (Howarth, McMichael, and Sharpey-Schafer, 1948) should be reviewed.

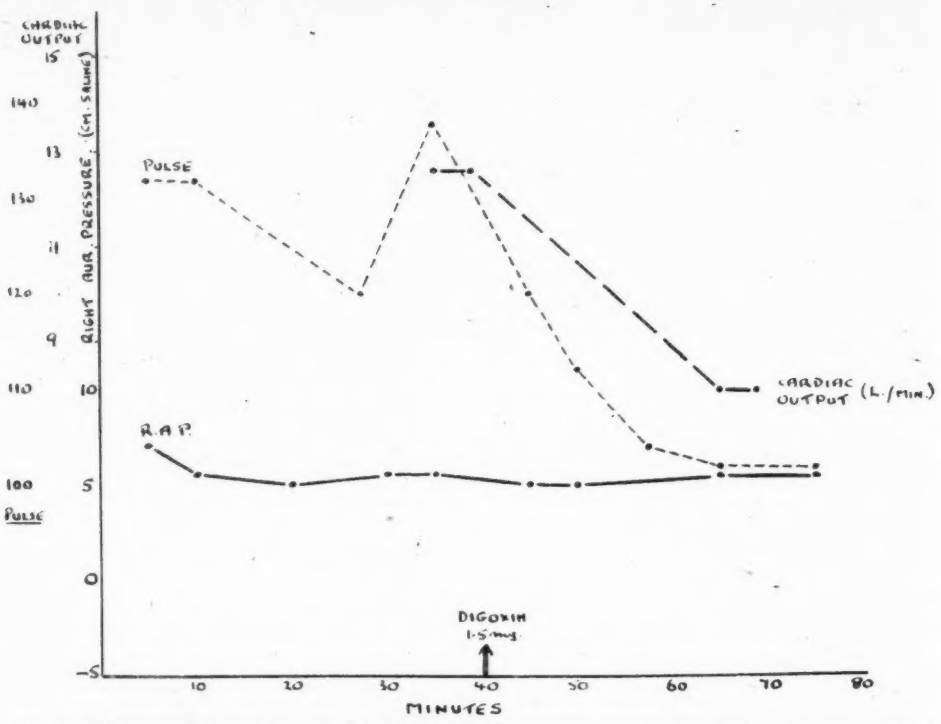

FIG. 4.—Thyrotoxicosis and anæmia. The effect of intravenous digoxin in a case of thyrotoxicosis and anæmia. The fall in cardiac output parallels the fall in pulse rate, but there is no change in the right auricular pressure. B.P. 205/100/50 throughout. Oxygen capacity 11·5 vol. per cent. Hæmoglobin 8·6 g. per 100 ml. Oxygen consumption 380 ml./min. R.V.P. 37 cm. saline. A-V difference 31–39 ml./litre.

SUMMARY AND CONCLUSIONS

The effect of digoxin on the venous pressure or right auricular pressure was investigated in four cases of classical congestive heart failure with normal rhythm and in twelve cases in which the venous pressure was raised for other reasons. These cases included anæmia, thyrotoxicosis, acute nephritis, artificial hydræmia, and chronic constrictive pericarditis. The dose of digoxin was 1·5 mg. intravenously in all instances.

In the four examples of congestive heart failure the venous pressure or right auricular pressure fell conspicuously within 30 minutes, and the cardiac output, when measured, rose.

In the twelve patients without congestive heart failure the right auricular pressure did not alter appreciably within 40 minutes. The cardiac output, when measured, was either unchanged or fell with the pulse rate.

A conspicuous pressor effect was demonstrated in most cases.

It is concluded that intravenous digoxin, in doses of 1·5 mg. intravenously, does not primarily lower the venous pressure, at least in the type of case described.

As a corollary, it is suggested that the effect of digoxin on the venous pressure in cases of congestive heart failure may yet depend upon its direct action on the heart, as originally believed.

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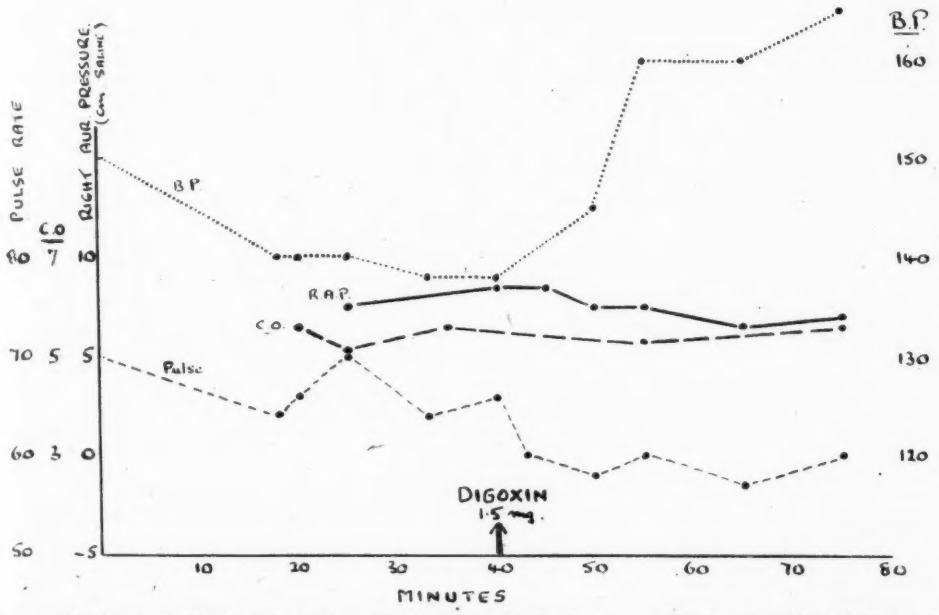

FIG. 5.—Acute nephritis. The effect of intravenous digoxin in a case of acute nephritis. There is no significant change in cardiac output or right auricular pressure, but there is a conspicuous rise of blood pressure. Oxygen capacity 16·9 vol. per cent. Hæmoglobin 12·6 g. per 100 ml. Oxygen consumption 257 ml./min. R.V.P. 20 cm. saline. A-V difference 46·5–51·5 ml./litre.

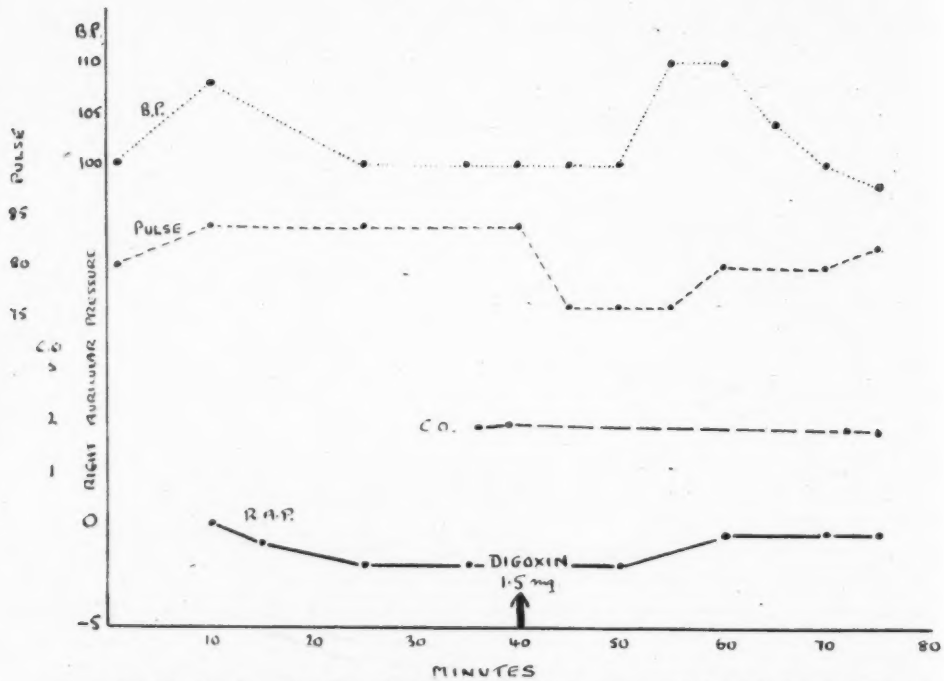

FIG. 6.—Induced hydræmia. The effect of intravenous digoxin in a case of induced hydræmia. There is no change in the right auricular pressure. The usual pressor and slowing effects may be noted. Basal oxygen uptake 208 ml./min. Oxygen capacity 161 ml./litre. Hæmoglobin 12 g. per 100 ml. R.V.P. 14 cm. saline. P.A.P. 24 cm. saline. A-V difference 105–115 ml./litre. Fourteen days preparation: NaCl. 10 g. daily. Water 10–12 pints. DOCA 25–50 mg. Gained 11 lb. Œdema+J.V.P.+2-3 at 35°. Some nausea and vomiting.

Fig. 7 and 8. See next page.

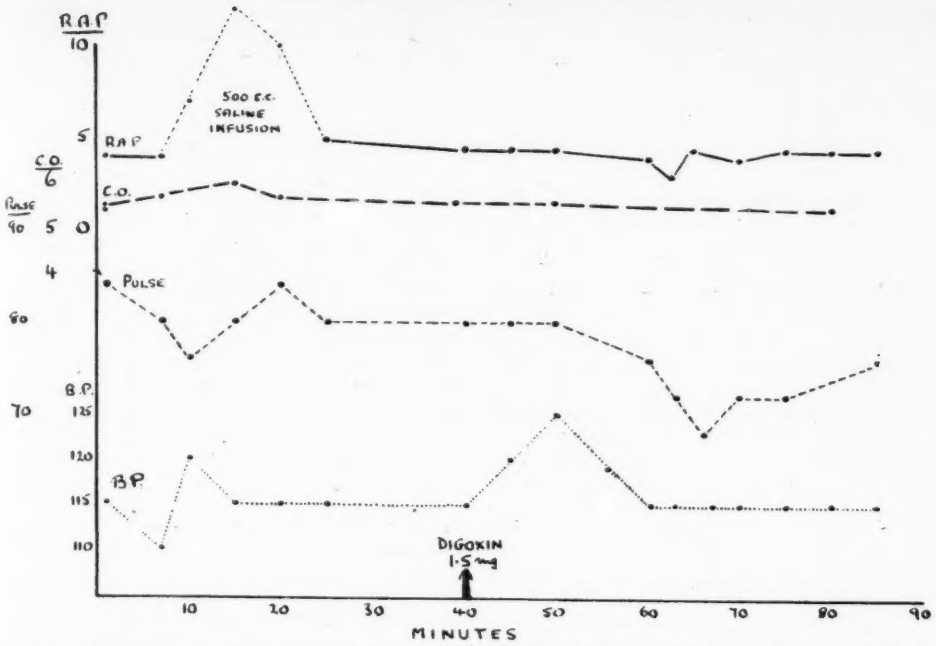

FIG. 7.—Pick's disease. The effect of intravenous digoxin in a case of Pick's disease. There is no change in the right auricular pressure. Oxygen consumption 286 ml./min. R.V.P. 10·5 cm. saline. Oxygen capacity assumed 20 vol. per cent. A-V difference 48–54 ml./litre.

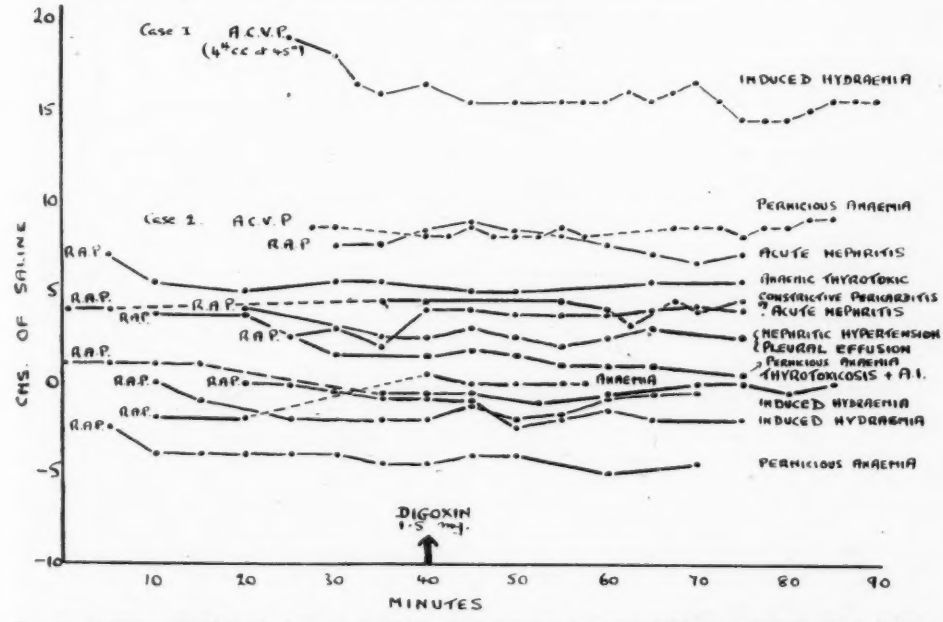

FIG. 8.—Absence of effect of digoxin on the venous pressure in cases without congestive heart failure. Superimposed charts illustrating the absence of appreciable change in the right auricular pressure as a result of digoxin in 12 cases characterized by a rise in venous pressure without heart failure.

PROCEEDINGS OF THE BRITISH CARDIAC SOCIETY

A special AUTUMN MEETING of the BRITISH CARDIAC SOCIETY was held at the Royal Society of Medicine, London on October 29, 1948. Chairman: JOHN HAY. The Chairman took the chair at 9.30 a.m.; 89 members and 38 visitors were present.

CHEST LEADS

TERENCE EAST moved the adoption of the report that had been prepared by Curtis Bain, I. G. W. Hill, Paul Wood and himself at the request of the Council (see page 103).

The following members then took part in the discussion.

WILLIAM EVANS. Since the introduction into this country of unipolar chest leads they had been accepted as ideal on theoretical grounds. Doubtless in time things would sort themselves out, but in the meantime we must decide what helped us most when a patient with cardiac pain came to us for diagnosis. Leatham had made a valuable contribution to this subject and we could see more clearly what we should do in the future. The following points which had been the main outcome of this study and of the application of the three chest leads, CR, CF, and V, in actual practice.

(1) Since the T wave was so often inverted in CF leads in health, this lead should be discarded. (2) CR1 depicted the P waves better than did V1, and for this reason it was a better lead to use in arrhythmia. (3) Since the R wave was better portrayed in CR1 than in V1, it proved a better lead for the diagnosis of septal infarction. (4) Since the T wave was so often inverted in V1 in healthy adults, CR1 was a better lead to use in the diagnosis of right heart preponderance, for the T wave was seldom inverted in this lead in healthy adults. (5) Again, since the T wave in V leads was usually small at the chest stations 6 and 7, sometimes becoming flat or inverted in health, the CR lead was superior in that the T wave in CR7 was always upright in health.

For these reasons anyone who customarily used CR leads need not change to unipolar chest leads in the hope that they would gain additional information in clinical diagnosis, for they would be disappointed.

PAUL WOOD. A discussion on which chest leads are the best is not profitable, because they are all facets of the same thing: thus conclusions drawn after comparing CR, CF, and V leads are obvious if unipolar limb leads have been taken with any chest lead. The time had surely come to adopt unipolar leads in general.

The question of how best to mount the records might be trivial, but it seemed to be a problem that needed solution. The obvious way was to mount the chest leads around a diagrammatic section of the heart in the positions from which they were actually taken, and to set Einthoven's triangle about them, the unipolar limb leads appearing at the apices and the standard leads along the sides. This, however, was admittedly impracticable. The next step was to make a more schematic diagram of the heart in the centre of the triangle, so that the chest leads appeared in a horizontal straight line. This was also too laborious. The diagram of the heart could be omitted with advantage, the leads being placed as before with reference to Einthoven's triangle. Finally, the triangle could be dropped, and lead VF brought into line between leads II and III. The result was neat, and the individual leads could be easily picked out according to their geographical relationship to an imaginary Einthoven's triangle. Figures illustrating these suggestions were shown.

K. D. WILKINSON. Being old, I am not yet convinced that multiple electrocardiographic leads offer us greater security in the diagnosis of coronary occlusion. These leads, if taken, should be recorded in the simplest possible form, and it seems to me that we shall only reach a definite conclusion when, by combination, we have records of a large number of cases complete with electrocardiograms and the findings of autopsies. In the meantime, I want to stress the importance of taking a good history in every case.

MORGAN JONES. It is not claimed that the "unipolar" limb leads are precisely unipolar, so it is perhaps best to call them "extremity potentials." Goldberger's "augmented unipolar" limb leads have two advantages over the original Wilson leads: (a) the lead connections necessitate only one electrode on each limb, and (b) the potential changes are conveniently large. They omit the Wilson resistances, however, and Bryant and Johnston have

shown that this omission introduces significant error in a small percentage of cases. So, although Wilson adopted the Goldberger technique, he preferred to retain the resistances and this appears to be the most acceptable method for general use.

In recording either the præcordial or the extremity potentials, it is not correct to say that the resistances are unnecessary if the skin resistance is low; the purpose of the resistances is to prevent an appreciable flow of current when there is a considerable potential difference between points coupled together —they are therefore *more* necessary if skin resistance is very low. In practice, the resistances are naturally more advisable in recording extremity than præcordial potentials. The Wilson resistances have the same effect as a high skin resistance in increasing the tendency to pick up alternating current. To reduce interference when recording the classical limb leads, it has always been the custom to earth the "spare" limb through the instrument but, when either the central terminal or the Goldberger technique is used, all three limbs are required, so it is impossible to earth any of them. Therefore, to reduce interference, all switches designed for recording "unipolar" leads should incorporate a connection to the *right* leg which is constantly earthed.

The importance of using a considerable number of præcordial leads has been underestimated. These leads reflect principally the potential changes of a small part of the ventricular muscle adjacent to the electrode, so records from three or less positions may fail to show a lesion confined to part of the anterior ventricular wall. This is especially important in the recognition of anterior infarction, for only one of the six usual præcordial leads may reveal *diagnostic* abnormalities. In addition, multiple præcordial leads give valuable information concerning the extent of the infarct. Further, as the electrode is moved across the præcordium, the progressive changes in the ventricular complex form a regular pattern in normal subjects, and disturbances of this pattern from disease cannot always be recognized when the form of the complex is known only at two or three points. Finally, it cannot be over-emphasized that the right præcordial potentials rarely influence the extremity potentials, so that anteroseptal infarction is usually associated with a normal limb lead electrocardiogram.

After further discussion the Society then approved the publication of the Report as an expression of the present views of the majority of its members. [The Report is published on page 103 of this number.]

Short Communications

A Clinical Comparison of CR, CF, and V Leads in Health and Disease

By Aubrey Leatham

(*Introduced by* William Evans)

On 500 patients, including 100 controls, leads CR, CF, and V 1–7, standard limbs leads and unipolar limb leads have been taken. Analysis of the chest leads on a purely practical basis has led to four main conclusions.

Since the CF electrocardiogram so often appears abnormal in health it is best to forego it in routine practice.

In ventricular preponderance, bundle branch block, posterior cardiac infarction, and in most cases of anterior infarction, a comparison of the CR and V electrocardiograms showed that there were no significant differences between the QRS complexes and T waves.

In 30 patients with anterior or antero-lateral cardiac infarction showing slight cardiographic changes, the abnormalities were seen more plainly in the V leads, although in only one were they absent from the CR leads.

On the other hand, the T inversion commonly found in V1 in health and occasionally in V7 might be considered a disadvantage. In practice, therefore, neither electrocardiogram has shown much superiority over the other.

A Comparison of Standard Leads, Unipolar Limb Leads, and Præcordial Leads

By D. R. Cameron

(*Introduced by* J. H. Wright)

Standard limb leads, unipolar limb leads (Wilson and Goldberger techniques) and præcordial leads 1–6 of CR, CL, CF, and V (Goldberger) types were taken in 30 normal and 30 abnormal subjects.

The site of the remote electrode may have considerable effect on the form of the præcordial cardiogram. Any component—P, QRS, S-T or T—may be affected.

In the normal case, differences are usually most obvious in the extreme right (1 and 2) or left (5 and 6) positions, where the amplitude of the deflections is small and therefore more liable to noticeable distortion. They are also more obvious in P and T because (a) deflections are smaller, and (b) duration is longer than in QRS.

In certain abnormal cases, the differences may be most obvious in the transitional zone (3 and 4).

Prediction of the differences in CR, CL, and CF is possible from a study of any one of them in conjunction with the S limb leads (of Wolfirth and Wood).

The V leads always occupy an intermediate position between the extremes of the other præcordial leads, i.e. distortion is reduced to a minimum.

Consideration of the unipolar limb and præcordial leads renders possible a fairly accurate prediction of the CR, CL, and CF leads. In the normal cases the variations depend mainly on the position of the heart. In the abnormal cases they depend also on the nature and site of the lesion.

Preliminary study (6 cases) indicated no significant differences in V (Goldberger) and V (Wilson) præcordial leads.

The augmented Goldberger technique for unipolar limb leads seems in some cases to give larger amplitudes than could theoretically be expected, though the form of the complex is unaltered.

Unipolar Electrocardiograms in Coronary Thrombosis

By Anne C. Aitkenhead

(*Introduced by* J. H. Wright)

The present contribution deals with 150 cases mostly of coronary thrombosis studied by unipolar leads over the past three years. In most early cases, serial tracings were taken every few days and cases studied at the beginning of the investigation have been recalled for check-up. The cases have been classified according to localization of infarct after the method of Wilson and the relative frequency of the different sites has been noted.

While many fit into the well recognized groups, a considerable number are atypical, e.g. a typical T III electrocardiogram in standard limb leads may be associated with a *small* R in leads over right side of præcordium and not the usual large R. The coexistence of left ventricular hypertrophy is a complicating factor in leads over left side of præcordium but the height of R and the level of S–T help to differentiate.

Serial tracings have shown the regression of an infarct from its edges inwards; thus an antero-septal and antero-lateral infarct shows most rapid signs of healing in V6 and later V5 and also in V1 and later V2 while V3 or V4 may be the last to return to more or less normal. We have used V7 frequently and find it particularly useful in postero-lateral infarcts where it may be the only lead which overlies the infarct directly (albeit only its edge). Leads V5 and V6 are not infrequently redundant.

Cardiac Pain with Recovery of the T Wave

By Terence East and S. Oram

Published in full, Brit. Heart J. (1948), **10**, 263

The Effect of Posture upon Normal and Abnormal Electrocardiograms

By A. Morgan Jones, H. K. Hellerstein, and Harold Feil (*introduced*)

The effect of posture upon the standard limb leads, the extremity and præcordial potentials has been studied in 100 cases, 20 normal, 20 right, and 20 left bundle branch block, 20 with isolated right ventricular enlargement, and 20 with isolated left ventricular enlargement. Electrocardiograms were recorded in the supine, sitting, right and left lateral positions except in the cases with bundle branch block, in which the sitting posture was not studied.

In *normal subjects* the axis could be changed within wide limits in a considerable proportion of cases, sometimes over almost the whole normal range from +90° to 0°, but in no case did the axis fall outside normal limits in the postures studied. The axis was usually farthest to the left in the sitting posture and to the right in the left lateral position.

The changes were due to reversal of the form of the extremity potentials of the left arm and left leg; the præcordial potentials remained of the same general form, but the transitional zone rotated to the left when the axis in the standard limb leads shifted to the right. T wave changes were associated with the QRS changes.

In *left bundle branch block* very striking changes occurred, especially on turning into the left lateral position. In this posture abnormal right axis deviation appeared in 4 cases, and the limb lead cardiograms simulated right bundle branch block; the præcordial potentials remained substantially unchanged and in all positions were characteristic of left bundle branch block. The changes were much less striking in *right bundle branch block*, the limb leads being substantially of the same form in all positions.

In *left ventricular enlargement* even more striking changes were present, again most extreme in the left lateral position. In that position abnormal right axis deviation appeared, and ST–T changes appeared in lead III instead of in lead I, owing to reversal of the form of the extremity potentials of the left arm and left foot. The appearances in this position thus often simulated those of right ventricular enlargement, but the præcordial potentials remained characteristic of left ventricular enlargement. In cases with *right ventricular enlargement* the changes in the limb leads were very slight and did not simulate left ventricular enlargement in any position.

The striking postural changes in left ventricular enlargement and in left bundle branch block were compared with the slight changes in right ventricular enlargement and right bundle branch block. If the amount of axis change is taken as an indication of the extent of the changes in pattern, there is a statistically significant difference between the extent of the changes in left ventricular enlargement and in normal subjects on the one hand, and between normal subjects and right ventricular enlargement on the other. Possible reasons for this difference were discussed.

Subacute Bacterial Endocarditis

By K. D. Wilkinson

The Birmingham centre has treated 63 cases and has had 12 relapses. The *Streptococcus viridans* is the infecting organism in over 90 per cent of cases. Fifty-eight per cent of all cases have been cured and are alive, many at full work as before their infection.

When the centre began we used a dosage of 0·25 mega units daily and met 4 cases with infections that could not be controlled. With a dosage of 1 mega unit daily for 28 days the results have been better. For a relapse 2 mega units daily for 6 weeks is the usual dose, but for one highly resistant *Streptococcus D* a dosage of 11·5 mega units daily for 6 weeks resulted in a cure. There have been no failures to cure the infection with the bigger doses.

The initial symptoms of a relapse may be very slight: as patients are under supervision the relapses are detected early and treated efficiently and early. It is probable that the early symptoms of most cases of infective endocarditis are slight, and it seems most important to point out the early symptoms so that all cases may be investigated and brought under treatment as early as possible.

A change in health is the first thing noticed. Fever, seldom high; sweating, especially at night; malaise, lassitude, and vague pains in back or limbs which is commonly diagnosed as influenza. Some anorexia and loss of weight occur, but these symptoms tend to be slight and vague. Even those who have had a similar illness before tend to say "I don't feel well."

The physical signs may be almost as slight and vague. Splenic enlargement and changes in the heart murmurs are among the most definite. Major embolic manifestations are unusual but intermittent albuminuria with blood cells and casts in the urine are quite the most frequent significant sign.

There were 2 cases of hemiplegia, 1 of aphasia with no other definite nervous lesion, 2 of repeated pulmonary embolism, and 1 with glycosuria which disappeared as the infection was brought under control.

The best results are obtained in those who come under treatment early. The mouth is far the most important source of infection: in eight of this series the extraction of teeth was related to the onset of symptoms so definitely that there can be no doubt that the operation acted as a trigger, but gingival infection is at least as important as apical abscesses. The patient with the resistant *Streptococcus D* whom I have mentioned as cured by 11·5 mega units daily for 6 weeks began to respond after an extensive excision of swollen infected gingival margins.

Teeth and gingival infection can be treated while the patient is on the penicillin course, and this is

very important if relapses are to be avoided. As might be expected, the blood urea gives some indication of the severity of renal damage. Those patients with raised blood ureas do less well as a rule. Hæmoglobin estimations are important. Bramwell stated in his recent paper that the rate of hæmoglobin recovery was slow: recalling a few individual cases I doubted this, but on working out the recovery curves of all our cases I find that the observation is perfectly correct. The blood recovery rate contrasts most remarkably with the results of iron therapy in low colour-index anæmias or liver treatment in typical Addisonian anæmia. In cases of infective endocarditis who had no hæmatinics or transfusion in the first month the average gain of hæmoglobin is 3·5 per cent, i.e. from 76 to 79 per cent. In the second month all the records tend upwards, the average gain being 8 per cent, i.e. from 79 to 87 per cent; while in the third month the rise was 7 per cent, i.e. from 87 to 94 per cent.

Mitral Stenosis in Later Life

By Harold Cookson

Results of observations on 36 cases with mitral stenosis ranging in age from 51 to 77 years were reported. Women outnumbered men by 3 to 1, and most of the patients were seen in private practice. A clear history of rheumatic fever or chorea was given by 13, and in a further 8 heart disease or a valve lesion had been diagnosed in early life. In 4 cases the first known attack of rheumatic fever occurred at the age of 34 or later.

All patients had lead normal active lives up to the sixth, seventh, or eighth decade, and 15 of the 21 married women had had children. When first seen 32 patients had auricular fibrillation, and 2 auricular tachycardia, and the onset of an arrhythmia seems nearly always to coincide with the first appearance of symptoms. Hypertension was present in a high proportion.

The criteria of diagnosis were given. The X-ray appearances of the heart and great vessels, which differ in some ways from what has been regarded as the characteristic picture of mitral stenosis, were described. Prognosis, cause of death, and necropsy findings (3 cases) were dealt with. The ætiology of the valve disease was considered to be rheumatic in all cases, and the reasons for the latency of the lesion until late in life was discussed. Reasons were given for thinking that the diagnosis of mitral stenosis in later life is often missed.

An Artificial Circulation

By R. J. S. McDowall

This artificial circulation is a robust piece of apparatus which has been in use by medical students for a year. By means of it, the main mechanical features of the circulation of the blood may be shown.

The pump has the special feature that its output can be shown to depend both on its input and to a limited extent on the frequency of its stroke. It consists essentially of a piece of flattened bicycle 1-inch inner tubing 4 inches long which is compressed by a moving plate controlled by a cam. A large inlet "valve" of little resistance is provided by the closure of the inlet by a narrow plate driven by another cam on the same shaft just before the main stroke of the pump. A very robust and simple exit valve is provided by a piece of inner tubing stretched over a piece of brass tubing into the outer end of which is inserted a wider flat piece of bakelite. A visible flow indicator in the system is provided by a bent tube inside a small Kjeldahl flask, the flow being directed against the side of the flask to avoid frothing.

The rate of the pump can be altered by changing the starting resistance of the motor driving the camshaft and the effects of tachycardia shown.

The "arterial" pressure taken on a mercury manometer can be altered up to 200 mm. Hg by changing the filling of the heart, its rate within limits, and by varying the resistance of the system. Increased filling of the heart is produced by raising the hinged part of the system to the horizontal or by compressing the "blood depot" which is a piece of inner tube which can be rolled up. The air pressure can be adjusted in the bottle so that the changes in "heart" output become visible.

The "venous pressure" taken on a manometer (a narrow burette with a fountain-pen cap as a piston), can be shown to be affected by the amount

of circulating fluid, by the capacity of the system, which can be increased by unrolling the "blood depot," by the peripheral resistance, and by the output of the pump. If the pump is slowed or stopped, the "venous pressure" rises markedly as in cardiac disease.

A reduction of the elasticity of the system to imitate hardened arteries provided by the inverted bottle is effected by pinching the tube and is shown to increase the pulse pressure and render the flow in the flow-meter intermittent.

A lever system from the rubber valve chamber may be added to record the rapid changes in the "arterial pressure" better than the mercury manometer.

For making original forms of the pump and the exit valve I am particularly indebted to Dr. A. E. Schuster.

The Effect of Digitalis on the Venous Pressure

By Paul Wood and John Paulett (*introduced*)

Published in full, Brit. Heart J. (1949), **11**, 83

Heart Failure and Tricuspid Incompetence

By W. Brigden and E. P. Sharpey-Schafer

It was shown previously that in cases of tricuspid incompetence mean right auricular pressure was higher than the mean pressure in a peripheral vein, a phenomenon that can be reproduced in a simple mechanical model. In cases with tricuspid incompetence it may be difficult to decide to what extent the high venous pressure results from incompetence or from heart failure. Manometric curves of right auricular pressure show a high systolic curve and indicate the diastolic pressure level. Continuous recording of pressure waves on rapid withdrawal of the catheter from auricle to peripheral vein show damping out of the systolic pulsations in the peripheral vein. The presence or absence of heart failure may also be demonstrated by measuring the response of the forearm flow to changes in posture. In the normal subject the forearm vessels constrict on tipping into the upright posture, while in cases of left heart failure, with or without high right auricular pressures, constriction occurs in the supine position. Some cases of tricuspid incompetence show the same response of the forearm vessels as the normal subject to changes in posture, although systolic and mean right auricular pressures are high.

Angiocardiography in Congenital Heart Disease

By Maurice Campbell and T. H. Hills (*introduced*)

The apparatus consists of a special trolley over which an X-ray tube is located at a suitable height. Just below the trolley top is a 15 by 16 inch fluorescent screen and the image produced at this plane is recorded by a large roll-film camera.

Exposures are made at the rate of one a second on a film whose width is such that the finished negatives are about 5 by 5 inches square. As many as fifty consecutive exposures could be obtained but in practice the number is normally limited to fifteen.

The opaque medium used is a 70 per cent solution of diodrast in water, and a preliminary sensitivity test is carried out.

Success depends on the intravenous injection of from 30 to 50 ml. of the dye in a maximum of 2 seconds. It is usually necessary to expose a vein in the arm and insert a wide gauge canula. A preliminary injection of 20 ml. of saline demonstrates the suitability of the vein and the speed with which the injection can be made. About five seconds after the injection the patient feels a sensation of heat which reaches its maximum rapidly and fades more slowly within two minutes.

It is not practicable to carry out this investigation in small or nervous children without an anæsthetic, and this must add to the risk. The best anæsthetic is probably the combination of cyclopropane and oxygen. Oxygen should be continued till normal conscious respiration has been restored.

In Fallot's tetralogy the interpretation of the films can be considered under two headings.

Firstly, the volume shunt of blood from right to left is estimated by the degree of filling of the aorta which is generally seen as early as two seconds after the injection. The presence of dye in the subclavian artery, the abdominal aorta, and the kidneys gives additional direct evidence of the proportion of dye taking this route.

Secondly, the pulmonary arteries usually show some filling at about two seconds but the degree of stenosis cannot be assessed on this time basis alone. If there is much flow of dye through the lungs their general density will show a steady increase to a maximum in about eight seconds. This estimation of the changing density of the lung fields would appear to be a more valuable observation than the actual time and degree of filling of the pulmonary arteries.

The first film of the series will often show some venous backflow due to a temporary rise of venous pressure. Traces of dye may be seen in the inferior vena cava and the internal jugular vein. This abnormal pressure must be taken into account when estimating any volume shunt but is not likely to persist after the first two seconds.

In cases that appear to be typical instances of Fallot's tetralogy evidence of a right to left shunt has been obtained regularly. In one case thought to be Fallot's tetralogy no right to left shunt was found and post-mortem there was high grade pulmonary stenosis with a small auricular septal defect without the other features of Fallot's tetralogy. A moderate right to left shunt has sometimes been suggested in cases that were not obviously cyanotic.

Our early clinical impression is that the method is perhaps less sensitive in detecting pulmonary stenosis, presumably in cases where this is not so severe. This differentiation may prove of value in estimating the degree of success following a systemic-pulmonary anastomosis or in chosing cases suitable for pulmonary valvulotomy.

In addition, a high proportion of angiocardiograms show points of interest that were not suspected—a double superior vena cava, a large pulmonary artery on one side with obstruction on the other side, and a widespread venous anastomosis on the right side. In one case regarded as tricuspid atresia with non-functioning right ventricle the angiocardiogram provided good supporting evidence.

Circulation Times in Congenital Heart Disease

By K. D. Allanby

(*Introduced by* Maurice Campbell)

To be published in full, Brit. Heart J., April, 1949

Apical Diastolic Murmurs in Severe Anæmia

By H. E. S. Pearson

A murmur closely simulating that of mitral stenosis can occur occasionally in cases of severe chronic anæmia in the absence of valvular disease. Numerous references to this are found in late nineteenth century continental textbooks and articles on pernicious anæmia, and Cabot (1896) recorded 9 such murmurs in his series of 857 cases of this disease. Gunewardene (1933), dealing with hookworm anæmia, describes 4 cases in whom a confident diagnosis of mitral stenosis was disproved either by autopsy or by the disappearance of the murmur on treatment, and Klinefelter (1942) obtained graphic records of apical presystolic murmurs in patients with sickle-cell anæmia.

Three cases presenting this physical sign are described, and the apparently arbitrary appearance and fugitive nature of the murmurs are shown by means of charts. This murmur has several features in common with the transient diastolic murmur that can occur in cases of rheumatic fever (Carey Coombs, 1924) and in discussing its possible cause certain explanations that have been put forward for the latter are admissible here for consideration.

With these inclusions, the following factors have been held responsible by various authors.

1. Decreased viscosity of blood (Sahli, 1895; Garb, 1944).

2. Increased speed of blood flow (White and Wood, 1923) with rapid filling of atonic left ventricle (Bland, Jones, and White, 1935).

3. "Relative mitral stenosis" (White, 1937), or combination of these (Luisada, 1948).

4. Pressure of dilated pulmonary artery on mitral orifice (Kerr, 1936).

5. Pressure of dilated right and left ventricles on mitral orifice (Weinstein and Lev, 1942).

It is felt that the facts observed in these three cases cannot be satisfactorily explained in any of the above ways, although the first factor may play a part. The suggestion is made that the apical diastolic murmur in severe anæmia is caused by incomplete opening of the mitral valve, associated, in the way to be described, with loss of passive tone in the papillary muscles.

The stream of blood, entering the ventricle axially, recoils radially and upward towards the base of the heart, thus tending to press the mitral cusps together. Closure is prevented chiefly by the lateral pressure of the entering stream but also by the passive tension of the papillary muscles on the chordæ tendinæ. Only minor pressures are involved and failure of the papillary muscles to exert their normal light " spring-loading " action on the valve allows the cusps to lie so sharply curved towards one another that a murmur is produced in the narrowed commissure. Fatty change, when present, is commonly maximal in the papillary muscles, and may lead to stretching.

This paradoxical movement and its control by the papillary muscles can be demonstrated in the cadaveric heart by a simple experiment.

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The Graphic Registration of Basal Diastolic Murmurs*

By Bertrand G. Wells

(*Introduced by* Geoffrey Bourne)

The vibrations of the diastolic murmur of aortic regurgitation are of high frequency and very low energy value. Other cardiac events, however, cause at the same location vibrations of lower frequency and many thousands times the energy. If the phonocardiogram were to register deflections of amplitude directly proportional to the energy of these vibrations the tracing would have to be hundreds of metres wide in order to show the diastolic murmur as deflections of 1 mm. in width. If the amplitude of the low frequency waves is attenuated logarithmically with regard to their frequency, we are enabled to show the 1 mm. diastolic vibrations clearly while the low frequency waves are all reduced in amplitude by this process of filtration, so that they can be confined to paper a few centimetres wide. Workers in phonocardiography have almost always used unsuitable apparatus, and have not been able to register this murmur satisfactorily. We have used a Sanborn phonocardiogram with stethoscopic and logarithmic registration, and interchangeable chest pieces, and have, with due attention to technique, been able to register every murmur audible clinically.

An analysis of 50 consecutive cases with audible murmurs of aortic or pulmonary regurgitation showed much variation in pattern. The frequency of the vibrations varies from moderately low to moderately high. The murmur usually persists throughout most of diastole. The configuration is that there is usually an early crescendo phase before the longer decrescendo phase. This phenomenon is sometimes audible, but much more frequently registered, and failure to hear the early crescendo phase may be explained by study of the characteristics of the human hearing mechanism. Examples of all types of basal diastolic murmur are shown, excluding the continuous murmurs of patent ductus, A-V aneurysm, and venous hum. Occasional tracings are found where diastolic vibrations are registered when no murmur is audible. The significance of these vibrations is obscure, but their

evaluation is helped by a comparison of their pattern with that of the audible diastolic murmur.

Finally, since there is often difference of opinion among cardiologists as to whether a diastolic murmur is present or not, we consider that phonocardiography with proper technique may be of value in settling questions of this kind.

* This study was made while on a Cabot Fellowship, and with the assistance of Mr. Maurice Rappaport, and Dr. Howard Sprague of Boston, Mass., U.S.A.

Simple Calibrated Phonocardiography

By G. J. Aitken (*introduced*)

Knowledge of the frequency response of a phonocardiograph is necessary before records can be adequately interpreted. Even then, comparison with records of other instruments is difficult. Lack of this knowledge resulted in disagreement among earlier investigators. With instruments introducing attenuation of low frequency vibrations, heart sounds appear shorter, and the third sound and possibly important low frequency components of murmurs are recorded less frequently than with instruments that register low frequency vibrations well. The higher frequency murmurs, however, are more easily recorded and their moment of onset defined with just such attenuation of confusing high intensity low frequency cardiac vibrations.

A simple calibrated phonocardiograph is described. Basically it is a stethoscopic phonocardiograph with electrical filters enabling records to be obtained of vibrations in a "low frequency band" of 20 to 200 cycles a second, and in a "high frequency band" of 140 cycles a second upwards. It offers a fairly satisfactory solution to many difficulties in interpretation of single recordings. The precise frequency characteristics of the basic phonocardiograph are less important. Whatever the likely degree of attenuation of the low frequency components of the cardiac vibrations in the unfiltered phonocardiogram, they are easily recorded at suitable amplitude in the low frequency band, in the absence of all high frequency vibrations.

In the band embracing frequencies greater than 140 cycles a second the predominantly higher frequency of most systolic and diastolic murmurs allow them to be recorded uninfluenced by the high intensity low frequency heart sounds. The first heart sound is represented by sharply defined overtones of its second and third components, more suitable points from which to time auricular or ventricular systolic murmurs than any so far described.

Examples illustrating the value of simple calibrated phonocardiography are given.

A Case of Polyarteritis Nodosa showing Multiple Coronary Aneurysms

By John R. H. Towers

The case described is one of polyarteritis nodosa. For years the presence of palpable nodules was regarded as an essential diagnostic criterion in this condition, but recently it has been recognized that palpable lesions of this type are the exception rather than the rule. In this case the diagnosis was not so difficult but the clinical and autopsy findings were so striking as to be of interest.

The patient, a motor mechanic of 39, had no important illness until 1943, when serving in the 6th Airborne Division, he developed a duodenal ulcer, which gave rise to intercurrent dyspepsia and finally to his discharge in 1945. He had intermittent dyspepsia over the last two years, but remained at his work until May, 1948, when he suddenly developed pains in both legs and difficulty in walking, and he had to go to bed. Symptoms were first noticed whilst getting into a motor car. These pains were present from the knees to the feet. A few days later the pain became generalized; his hands and feet and testicles became slightly swollen and painful. There was in addition, swelling of the left breast which was very tender.

A fortnight after the onset he was free from pain and feeling better. A week later, however, he noticed his stools were black and he developed epigastric pain with some vomiting. This pain was worse before meals and relieved by food, but liable to occur at any time of the day or night and to last for several hours; at times it was very severe.

At this stage, i.e. three weeks after the onset, he had an attack of diplopia lasting half an hour; there was no previous attack and none since. After this there was a return of generalized aches and pains in the limbs and back; his appetite diminished and he lost much weight. His skin, normally rather

deeply pigmented, became darker in colour and he developed a sallow complexion. His sleep was disturbed by pain. Bowels a little constipated; micturition normal. These symptoms continued unaltered until his admission to the Leeds Infirmary in July, approximately ten weeks from the onset.

Examination on admission. He was cachetic with pigmentation of the skin, rather suggestive of Addison's disease. He had obviously lost much weight. He was pyrexial up to 101° for four days and thereafter there was no rise of temperature. His pulse rate averaged 100 until a day or two before his death. He had what were taken to be shotty glands in the neck, axillæ, and groins, and the spleen was just palpable. The blood pressure was 130/100. The urine contained a trace of albumen, but no red cells. The heart was not enlarged.

The blood count showed an anæmia without eosinophilia—Hb. 71 per cent; red blood cells, 3,700,000; white cells, 9,600; basophils, 5 per cent; polymorphs, 74 per cent; eosinophils, 2 per cent; lymphocytes, 20 per cent.

The X-ray of stomach and duodenum showed an appearance consistent with duodenal ulceration. The stools were negative for occult blood. The Wassermann reaction was negative.

Extensive investigation was carried out with no helpful finding, but shortly we discovered that the so-called glands extended down the arms, along the line of the vessels and also to a lesser extent, down the inner aspect of the thighs, and a hard, shotty mass, the size of a pea was felt through the anterior rectal wall. *Biopsy* of one of the masses from the arm showed it to be a thrombosed aneurysm arising from a small muscular vessel, the wall of which showed extensive mucoid degeneration. The diagnosis of periarteritis nodosa was then made. The patient went gradually downhill, became emaciated, and died in September, 1948.

Autopsy. This was performed by Dr. Carmichael and showed a striking picture. A very large number of aneurysms ranging in size from 1 cm. to 2 cm. were seen in association with most of the principal arteries in the body, with the exception of those in the lungs and brain. The lesions have all relatively thick fibrous walls and are filled with dense thrombus, mostly of dark red colour but there are also masses of pale greyish-white clot or laminated grey and red clot clinging to the walls of many of the sacs. Few of the aneurysms are attached to vessels large enough to be opened up with scissors, i.e. they apparently spring rather from relatively small unnamed branches than from the larger trunks.

Impressive examples were as follows: a number of aneurysms adhering to the outer surface of the thoracic aorta and related to the intercostal arteries; a small vessel on the surface of the diaphragm at the attachment to the pericardium, where six close-set aneurysms, each 3 mm. in diameter were concentrated in 3 cm. of the vessel's length; a " beading " of the anterior aspect of the bony spine by aneurysms; and numerous aneurysms along the length of the spermatic arteries.

There are many large aneurysms on the right and left gastric arteries to the gastroepiploic artery. The mesentary also shows dozens of aneurysms of a size varying from 2 to 3 mm. to nodules almost 1 cm. in diameter. The aneurysms related to the stomach measure 1·5 cm. and more. The pelvic mesocolon shows only a very few small aneurysms and the position is similar with most of the arteries supplying various parts of the colon. Right, relatively large branch of hepatic artery bears a large aneurysm, 1 cm. in diameter, which is on the main stem, but there are several other similar sized aneurysms in this neighbourhood. There are several aneurysms of 2 cm. diameter and smaller within the head and body of the pancreas and at least two of these have ruptured, but the effused blood does not extend far into the adjacent tissue. There are few aneurysms in the vicinity of the abdominal aorta. The aneurysms are present on the branches of the splenic aorta in the hilum and substance of the spleen, and of branches of the renal aorta within the venal substance; also in considerable number of small size in the very large portal tracts. No aneurysms on main splenic and renal arteries.

The spleen contains an aneurysm fully 1 cm. in diameter and one or two smaller nodules and an infarct at one pole. The kidneys contain numerous thick-walled aneurysms approximately 3 to 6 mm. in diameter and located chiefly in the region of the boundary zone or farther in towards the hilus. There is also much recent infarction, and much irregular coarse pitting on the outer surface, probably due to scarring from an old infarction. The renal tissue otherwise is mottled, mostly showing a dusky congestion; other parts are pale. Large tracts of tissue are partially fibrosed.

The stomach was normal apart from well-marked engorgement at the crest of the mucosal folds in places and some hypertrophy of the pylorus and large area of scarring centred over the pylorus and lesser curvature, and spreading into the stomach and duodenum.

The brain and lungs, however, were normal, showing no gross change in their substance or vessels.

There are numerous aneurysms connected with the coronary branches, particularly the arteries supplying the line of the interventricular sulcus, and the anterior and lateral surface of the right ventricle.

At least 30 to 40 aneurysms of varying sizes are present, varying from a few mm. to 2·5 cm. in diameter. There is a thin layer of fibrinous exudate scattered over the whole epicardial surface. The chambers of the heart are all slightly dilated, but the myocardium has a healthy appearance and texture and shows no evidence of infarction.

Electrocardiographic Studies in Cretinism

By Bernard Schlesinger and Bernhard Landtman (*introduced*)

To be published in full, Brit. Heart J., July or October 1949

A Case of Pheochromocytoma with Sustained Hypertension

By Leslie Cole

This case is described to emphasize the fact that tumours of the adrenal medulla may cause sustained hypertension in the early stages, without giving rise to paroxysmal symptoms, or paroxysmal hypertension; to show the clinical picture in the early stages; and to comment on the use of certain diagnostic aids.

The patient was a farmer's wife aged 35, with three children, and she developed sudden headache three weeks after a severe antepartum hæmorrhage. This persisted daily almost without remission until her death thirteen months later. It was marked in the early morning, grew worse month by month and latterly was associated with early morning nausea, vomiting, profuse sweating, cold hands and feet, shakiness, nervousness of an unusual sort and "peculiar sensations"; and during the last three weeks, muscular weakness and exhaustion. The blood pressure was first found to be raised seven months after the onset (180/130) and remained steadily at this level until just before death. Repeated clinical examination was otherwise negative and thorough investigation failed to show any cause. A single paroxysm of hypertension seven days before death (260/150) revealed the probable diagnosis, but came too late to save her life. It was followed by a severe attack of right-sided abdominal pain and paralytic ileus which necessitated laparotomy and cæcostomy. At operation, a tumour was found at the site of the left suprarenal gland which subsequently proved to be a typical pheochromocytoma. This was removed a week later but the patient succumbed. Autopsy showed that the right-sided pain was due to a large infarct of the right kidney.

Diagnosis is difficult and involves recognition of the syndrome produced by hypersecretion of adrenalin and localization of the tumour or tumours. For the first, it is essential to realize that sustained hypertension is indistinguishable from the essential or malignant type and without paroxysms may be present in the early stages, and also to appreciate the significance of the symptoms illustrated by this case. In this and many others recorded there are unique clinical grounds for suspecting the diagnosis once the clinician is aware of the syndrome. Goldenberg's benzodioxane test then appears to be of great value in confirming it, but this patient died before his paper had been published. To localize the tumour, an intravenous or retrograde pyelogram may be sufficient, but perirenal insufflation may be necessary, or even exploration. Here, although the symptoms and signs pointed to a right-sided lesion, the tumour was on the left. Early diagnosis and accurate localization are extremely important because successful removal may be expected to give complete cure.

The Q–T Interval in Acute Rheumatic Carditis

By D. G. Abrahams

(*Introduced by* Paul Wood)

To be published in full, Brit. Heart J., July or October 1949

MULTIPLE UNIPOLAR LEADS

REPORT OF THE COMMITTEE OF THE BRITISH CARDIAC SOCIETY

The British Cardiac Society at its recent meeting approved the publication of the following report as an expression of present views of the majority of its members.

The Council had asked the committee, consisting of Terence East, I. G. W. Hill, Curtis Bain, and Paul Wood to draw up such a report that might help those who wished to have information about present practice. Obviously, they have no wish to limit in any way investigations into new and important methods but feel that where routine work, rather than research, is concerned, there are advantages in some degree of uniformity in leads presented, and in the way they are mounted.

It is, perhaps, too soon to reach any final recommendation in this last direction and various suggestions made at the meeting were considered (see Proceedings, p. 92). The Editor would be grateful if those submitting papers would generally try to use one or other of these methods, and a figure that is 4½–5½ inches wide is generally easier to print and better looking than one that is tall and narrow.

EDITOR.

REPORT OF COMMITTEE

Although multiple leads from a series of points across the præcordium are in general use in this country, there is so far only one position for the præcordial electrode defined as standard. Single præcordial lead used as routine may afford scanty or even misleading information, and multiple leads are essential.

Bipolar chest leads. It is suggested that the use of the bipolar chest leads CR and CF be discontinued. The distal electrode in the case of CR introduces a positive error, and in the case of CF an error that may be positive or negative, depending on the position of the heart.

UNIPOLAR CHEST LEADS

Unipolar V leads avoid this error. The switch is set for lead 1. The exploring or præcordial electrode is attached to the left arm wire of the cardiograph. It is then paired with a central terminal (right arm wire of the cardiograph) connected to the right arm, left arm, and left leg. The potential of the central terminal will practically be zero, by Einthoven's formula, as shown by experiment. The original method of Wilson connects each of the limbs to the central terminal through equal resistances of at least 5000 ohms. The method of Goldberger omits the resistance.

The Burger suction electrode (2 cm. in diameter) is convenient for the exploring præcordial electrode.

Positions. The position of the præcordial electrode is indicated by a numeral used according to the following plan. V1 shall be used for the right margin of the sternum, in the fourth intercostal space: V2 for the left margin of the sternum at the same level: V4 for the mid-clavicular line in the fifth intercostal space: V3 for a point midway between 2 and 4: V5 for the left anterior axillary line: V6 for the mid-axillary line; positions 5 and 6 are on the same level as 4: V7 is the posterior axillary line; and V8 below the apex of the scapula at the same level.

VE is used for an epigastric lead below the xiphisternum.

RUA stands for a position on the right costal margin just to the right of the midline.

The corresponding V positions to the right are shown by the letter R, e.g. V3R.

Standardization. As the voltages of V leads are often high it may be convenient to use half standardization (1mV = 5 mm.) in order to confine the deflections to a convenient size. If this reduced sensitivity is used it should be employed uniformly in all chest leads, and indicated N/2.

UNIPOLAR LIMB LEADS

The augmented unipolar limb leads of Goldberger are obtained by putting the exploring electrode, attached to the left arm wire of the cardiograph, the switch being set for lead 1, on the appropriate limb.

The other two limbs are connected to the central terminal, which is attached to the right arm wire of the cardiograph. The deflections are 50 per cent larger than those obtained by the Wilson method. The Goldberger technique is satisfactory. The tracings are labelled a VR, a VL, a VF.

In order to correlate standard limb leads and unipolar limb leads, it is helpful to recall that lead 1 is VL–VR, lead 2 is VF–VR, lead 3 is VF–VL; and that by the Goldberger technique a VL is $\frac{1}{2}$(I−III), a VR is $-\frac{1}{2}$(I+II) and VF is $\frac{1}{2}$(II+III).

Selection of Leads

The full electrical exploration of the heart involves the taking of at least twelve leads, and sometimes more. The twelve basic leads are (1) the three standard limb leads, (2) the three unipolar limb leads, and (3) the six unipolar præcordial V leads.

Until familiarity with the appearances of the deflections in the various leads in different conditions is obtained, these twelve should be recorded as a routine.

In practice the taking of twelve leads is laborious and time-consuming, and involves the use of many films. It is possible to limit the leads recorded to a selected few when a particular lesion is suspected. Films may be economized also by exposing half a strip at a time when the Cambridge instrument is used, and so obtaining six tracings on one film.

The following suggestions may help in selecting leads likely to be most useful in the diagnosis of various lesions. For the preliminary routine approach it may be enough to select V1 or V2 and V4 and V5 or V5 and V6 depending on the size of the heart; and VL and VF. These may suggest what further records are needed for full electrical exploration. The clinical findings may suggest special leads.

It is important to record potentials from the surface of the left ventricle; this may necessitate the use of leads V6 or V7 when the interventricular septum is displaced to the left, or when there is clockwise rotation of the heart about its longitudinal axis (viewed from below).

Unipolar limb leads are particularly useful in showing the position of the heart; the combination of VL and VF is best for this.

VF shows auricular activity well, and so is useful for auricular arrhythmias; it is also useful for posterior infarcts.

VL shows lateral infarcts.

VR is of less value and may generally be omitted.

Right ventricular leads. V1 and V2

These show best:

1. Some infarcts of the myocardium
2. Right bundle branch block
3. Right ventricular hypertrophy
4. Massive pulmonary embolism
5. Auricular arrhythmias (V1 particularly).

Left ventricular leads. V4–6

These show best:

1. Some infarcts of the myocardium
2. Left ventricular hypertrophy
3. Left bundle branch block.

Myocardial ischæmia. V1 V2 V3 V4 V5 V6 VL VF.

Infarction can usually be detected and defined by V2–V6 and VL and VF. For high antero-lateral infarction records may be taken in the third and fourth interspaces vertically above V4, V5, and V6. VF is useful for distinguishing posterior infarction from other Q III patterns, particularly those due to transverse position of the heart, or to massive pulmonary embolism.

Bundle Branch Block. Right: V1 V2.

Left: V5 V6 V7, according to the degree of enlargement to the left.

Massive Pulmonary Embolism. V1 V3 V5 VF.

Pericarditis. V1 V3 V5.

Auricular Arrhythmias. V1 and VF.

Mounting of records. The V præcordial leads are most conveniently shown, horizontally in numerical order, with V1 as the first record.

Terence East. I. G. W. Hill.
Curtis Bain. Paul Wood.

ABSTRACTS OF CARDIOLOGY

Maternal Congenital Heart Disease as an Obstetric Problem. C. J. LUND. *Amer. J. Obstet. Gynec.*, 55, 244–261, Feb., 1948.

Details are given of a study of 25 cases of pregnancy complicated by congenital heart disease, 29 infants in all being delivered. There were 13 with a patent ductus arteriosus, 8 with interventricular defect, 4 with interauricular communications, 1 with pulmonary stenosis, and 4 of undetermined type. Toxæmia was a common and severe complication. Premature delivery took place in over 25%. Labour tended to be shorter than the average, and forceps delivery was resorted to in over one-third of the cases although half of the patients were multiparæ. All patients were classified according to the functional groups of the New York Heart Association, before pregnancy, during the first 3 months and the last 3 months, during labour, and later in the puerperium. The blood pressure, vital capacity, venous pressure, and circulation times were investigated in many of the patients. It was found that decrease of vital capacity was most valuable in prognosis. A sudden fall in blood pressure was noticed repeatedly soon after confinement and gave rise to considerable anxiety; the mechanism of this is discussed. A patent ductus arteriosus was found to be the most serious of the congenital cardiac complications. All but 1 of the cases of cardiac failure were associated with this lesion, as was also the only fatality.

Braithwaite Rickford

The Occurrence of Paroxysmal Cardiac Arrhythmia Following Air Embolism. C. GOBIN. *Arch. Mal. Cœur*, 40, 482–484, Nov.–Dec., 1947.

A student was entrusted with the operation of transfusing a donor's blood directly into the veins of a patient with septicæmia. He thrust the recipient's needle into the veins of the donor though fortunately failed to enter the veins of the septicæmic patient with the other needle. The subsequent attempts to carry out the transfusion caused the injection of about 200 ml. of air into the veins of the donor but no blood. The donor, whose arm veins became inflated was alarmed and eventually brought the operation to an abrupt end by pulling out the needle and releasing the tourniquet. His veins deflated but he was seized with a tickling sensation in the throat, with cough and violent dyspnœa. He lost consciousness for 4 to 5 minutes and did not recover his health for some days. For 5 months after this accident he was subject to attacks of paroxysmal tachycardia or palpitation lasting from a few seconds to a few minutes. The radiograph of his chest revealed a slight left ventricular hypertrophy. Eventually he had an attack of arrhythmia lasting for days and an electrocardiogram showed auricular fibrillation. He had no subsequent attacks and later acted again as a blood donor.

The author considers this to be an instance of an autonomic excitation initiated by the presence of air in the pulmonary vessels. *H. E. Holling*

Effect of Intravenous Cytochrome C on Capacity for Effort Without Pain in Angina of Effort. H. BAKST and S. H. RINZLER. *Proc. Soc. exp. Biol., N.Y.*, 67, 531–533, April, 1948.

Cytochrome C enhances the uptake of oxygen by the tissues. When injected intravenously it is capable of restoring to normal an electrocardiogram in which changes have been produced by inhalation of a 10% oxygen mixture. The authors have shown that cytochrome C in 50-mg. doses given intravenously to patients suffering from angina of effort is unable to increase their capacity for effort without pain. *A. I. Suchett-Kaye*

Treatment of Hypertensive Vascular Disease with Rice Diet. W. KEMPNER. *Amer. J. Med.*, 4, 545–577, April, 1948.

For the past 4 years the author has advocated a rice–fruit–sugar diet in hypertensive vascular disease and all forms of nephritis. This diet contains in 2000 calories, not more than 5 g. of fat, 20 g. of protein, 200 mg. of chloride, and 150 mg. of sodium. All fruits and fruit juices are allowed, sugar and dextrose are unrestricted, and supplementary vitamins are given. The effects of this diet on the blood and urine chemistry, blood pressure, heart size and electrocardiogram, œdema, and retinal arteriopathies in several hundred patients are recorded and illustrated by typical examples. [It is extremely doubtful if the inferences which the author draws from his data would stand up to strict statistical scrutiny.]

Henry Cohen

Coexisting Auricular Fibrillation and Complete Heart Block. E. A. HAUNZ and H. L. SMITH. *Amer. J. Med.*, 4, 237–242, Feb., 1948.

A series of 10 cases of auricular fibrillation and complete heart block, all in patients with advanced cardiovascular disease, were studied. The authors' two main points are that: (1) the presence of this combination, in the absence of a digitalis effect, implies a serious prognosis; (2) it is important to distinguish heart block due to intrinsic cardiac disease from that due to digitalis. In cases in which symptoms of digitalis intoxication are slight or absent the distinction can be made by observing serial electrocardiograms. *R. T. Grant*

Correlation Between the Effect of Quinidine Sulfate on the Heart and Its Concentration in the Blood Plasma. R. WÉGRIA and M. N. BOYLE. *Amer. J. Med.*, **4**, 373–382, March 1948.

It was found that after administration of a single oral dose of quinidine to patients with auricular fibrillation the effect on the circus rate of the auricle was roughly parallel to the quinidine concentration in plasma but no strict quantitative relation existed. For example, 2 hours after oral administration of 0·8 g. of quinidine sulphate the circus rate fell from 402 to 285 a minute and the plasma concentration of quinidine was 2·6 mg. per litre, whereas 10 hours after the administration of quinidine the circus rate was practically the same, 292 a minute, but the plasma concentration was only 1·3 mg. per litre. From a further series of experiments on dogs it is concluded that such quantitative discrepancies are due to the fact that the effect on the heart is not proportional to the concentration of drug in either the plasma or the myocardium. Indeed, an excessive increase in the concentration in heart tissue leads to a decrease in cardiac effect. *T. Semple*

Electrocardiographic Patterns of Ventricular Aneurysm. E. GOLDBERGER and S. P. SCHWARTZ. *Amer. J. Med.*, **4**, 243–247, Feb., 1948.

In a series of 40 cases of myocardial infarction with and without ventricular aneurysm, all the cases with aneurysm were associated with an upward QRS complex in the right arm lead of the electrocardiogram. This suggests that absence of this feature in a case of myocardial infarction indicates absence of aneurysm. *R. T. Grant*

The Arterioles of the Skin in Essential Hypertension. E. M. FARBER, E. A. HINES, H. A. MONTGOMERY, and W. McK. CRAIG. *J. invest. Derm.*, **9**, 285–298, Dec., 1947.

The authors review earlier studies on the arterioles of patients with hypertension, and present a comparable study of the arterioles of the skin. The wall to lumen ratio is lower in the hypertensive group, with a mean of 1·57 (70 cases), against 2·14 in the 52 control cases; there is, however, considerable overlapping. Moritz and Oldt (*Amer. J. Path.*, 1937, **13**, 679) have already shown that the thickening of the wall and narrowing of the lumen which commonly indicate a state of hypertension may be completely absent in cases with hypertension of long-standing. Conversely they find (in agreement again with Moritz and Oldt) that arteriolosclerosis may exist in the absence of hypertension and without any obvious correlation with age. *A. C. Lendrum*

Secondary Malignant Disease of the Heart. R. W. RAVEN. *Brit. J. Cancer*, **2**, 1–7, March, 1948.

This paper analyses 51 cases of secondary tumours in the heart or pericardium from the necropsy records of the Royal Cancer Hospital. The primary tumours were distributed amongst most of the organs of the body. Carcinoma of the breast was the commonest primary tumour (14 cases); secondary growth usually involved the pericardium, alone or together with the heart muscle, and was sometimes first manifested many years after radical extirpation of the primary tumour, periods of 5 and 16 years being recorded.

The pericardium was sometimes normal save for an isolated secondary tumour, but otherwise pericardial effusion, fibrous obliteration, or obliteration by massive deposits of tumour were found. Hydrothorax and ascites resulted from cardiac failure. The symptoms sometimes resembled those of subacute bacterial endocarditis. Dyspnœa, tachycardia, and cardiac irregularities such as auricular fibrillation or flutter were frequent outstanding signs. Some symptoms were attributable to the location of the tumour, causing heart-block, or to pericardial or pleural effusion but were not pathognomonic and further investigations were required to establish the diagnosis, including paracentesis for pericardial effusion and cytological examination of the fluid for tumour cells, radiological examination of the heart including tomography, and electrocardiography; the value of this last proceeding is emphasized. When the primary tumour is known to be radiosensitive, high-voltage *x*-irradiation may be useful in the diagnosis and treatment of cardiac secondary growths. *L. Foulds*

"Functional" Subclavian Arterial Murmur: Possible Relation to Scalenus Anticus Syndrome, Costoclavicular Compression, or the Neurovascular Syndrome of Wright. R. B. POMERANTZ. *Ann. Surg.*, **127**, 688–695, April, 1948.

In a routine examination of 2619 candidates in Texas the author discovered 20 females and 1 male in whom there was a systolic murmur over the subclavian artery (or arteries). The first 11 cases were dismissed as cases of functional murmurs, but the other 10 received more detailed examination. The murmur predominated on the left, appearing on that side alone 11 times; it appeared on the right side alone once, bilaterally 5 times, and in 4 cases the side was not noted. General medical examination and radiographs of the chest were negative, except in 1 case where there was inactive apical tuberculosis on the opposite side to the murmur. The murmur is constant, fairly loud and definite, and accentuated by deep inspiration or gradual abduction of the arm. The greater the abduction the louder the murmur up to 135 to 150 degrees, when it disappeared because the blood flow to the arm had ceased. No case was observed which was thought to be a scalenus syndrome, and in only 1 was the murmur thought to derive from costo-clavicular compression. The presence of the murmur when the subject is in a relaxed sitting position suggests some as yet undefined mechanism by which the artery is obstructed even before abduction begins. The preponderance on the left side would indicate an anatomical variation, but in the absence of symptoms surgical exploration was not thought to be justified and the question of causation is unsettled. *H. T. Simmons*

Elementary Atlas of Cardiography. H. WALLACE-JONES, E. NOBLE CHAMBERLAIN, and E. L. RUBIN. John Wright and Sons, Ltd., Bristol, 12/6.

This little book does not pretend to be anything more than its title implies. A short descriptive text introduces each series of cardiograms, which are beautifully reproduced and clearly annotated. However, no attempt is made to outline the elementary physics of electrocardiography, and a description of unipolar leads is entirely omitted. A brief essay on cardiac radiology precedes a well selected and representative collection of excellent radiograms, which includes all the more common cardiac conditions. The reproduction of these plates is of the highest quality, and indeed the whole volume reflects great praise on the publishers. The omission of an index is regretted. *J. L. Lovibond*

Seasonal Variations in Heart and Coronary Disease as Related to Various Environmental Factors. H. R. BROWN and R. PEARSON. *Amer. Heart J.*, **35**, 763–768, May, 1948.

A study of the vital statistics for the city of New York from 1934 to 1944 reveals that the death rate from heart disease, particularly coronary disease, is inversely related to the rise of monthly temperature, and not related to the relative humidity of the atmosphere. *H. E. Holling*

Experiences with a New Synthetic Analgesic, Amidone: Its Action on Ischemic Pains of Occlusive Arterial Diseases. R. J. POPKIN. *Amer. Heart J.*, **35**, 793–799, May, 1948.

"Amidone" (methadon, "physeptone") (6-dimethylamino-4, 4-diphenyl-3-heptanone hydrochloride), which resembles morphine in its action, was given to a number of patients with peripheral vascular disease who suffered from pain at rest. The dose was 5 to 15 mg. by mouth. The drug relieved the pain at rest but was ineffective in intermittent claudication. One of the 18 patients developed a hæmorrhagic urticaria and ambulant patients suffered from light-headedness, nausea, and vomiting. *H. E. Holling*

Effect of Sympathectomy on Blood Flow in the Human Limb. I. D. STEIN, K. HARPUDER, and J. BYER. *Amer. J. Physiol.*, **152**, 499–504, March, 1948.

A comparison was made by the use of plethysmographic methods of recording, of the blood flow in the foot (predominantly skin) and calf (predominantly muscle) in human patients, before and after sympathectomy of the lower limbs for peripheral vascular disease. The results show that, whereas the blood flow through skin was increased by sympathectomy, that through muscle was relatively unchanged. Exercise, local heating, and arterial occlusion and release were effective stimuli in increasing blood flow through sympathectomized muscles, suggesting that vasodilators of metabolic origin, and not the innervation, are important factors in the blood supply of muscles. The results indicate that sympathectomy is of value clinically for increasing the blood flow through skin, but not through muscle.

R. A. Gregory

Measurement of the Total Transverse Diameter of the Heart by Direct Percussion. W. D. STROUD, M. W. STROUD, and D. S. MARSHALL. *Amer. Heart J.*, **35**, 780–786, May, 1948.

In 333 examinations of 305 patients the transverse diameter of the heart as measured by direct percussion was compared with that obtained from a teleradiograph. 74% of the values obtained from percussion were within $\pm 10\%$ of the values obtained from radiography and 88% were within $\pm 15\%$ of the radiographic values. Fifty-five comparable examinations on 45 women gave similar results. The clinical method of percussing the heart size appears therefore to be of value. *H. E. Holling*

Perforation of the Infarcted Interventricular Septum. Report of Two Cases, one Diagnosed Antemortem. N. O. FOWLER and R. B. FAILEY. *Amer. J. med. Sci.*, **215**, 534–541, May, 1948.

Two cases of perforation of the infarcted interventricular septum are reported. In one of them the diagnosis was made during life. A review of reported cases revealed 56 similar, in 15 of which the diagnosis was made during life. The condition should be suspected in any patient who, shortly after a myocardial infarction, suddenly develops a systolic thrill and murmur in the third and fourth intercostal spaces just to the left of the sternum. These patients tend to develop right ventricular failure. In 38 cases the survival time was described, this being less than a month in 31. A further 6 patients died within a year, and 1 patient lived 4 years and 10 months. Out of 45 patients examined 43 had a systolic murmur, which in 22 was associated with a thrill. Rupture of a papillary muscle following infarction may be confused with this condition, but in the former the murmur tends to be heard best nearer to the apex, the patient's condition deteriorates rapidly, and the heart failure is left-sided rather than right-sided.

C. Bruce Perry

Blood Volume and Sympathectomy in Hypertension. W. D. DAVIS and H. S. MAYERSON. *Proc. Soc. exp. Biol., N.Y.*, **68**, 117–120, May, 1948.

Blood volume changes were investigated in 20 patients with hypertension who had undergone sympathectomy. There were 11 women and 9 men; their ages ranged from 22 to 50 years and the periods of follow up from 3 to 18 months. Plasma volume was measured photocolorimetrically with the T 1824 dye; whole blood and red cell volumes were calculated from hematocrit readings (Wintrobe). No consistent post-operative changes in the blood volume were found, and no consistent deviation from "normal" values was observed pre-operatively. It was noted that in 5 patients in whom the red cell volume was low before operation the response to sympathectomy was poor, whereas in 5 patients in whom the red cell volume was normal, or above normal, the results were good. In patients with long-standing vascular disease there was a tendency to low blood volume.

A. Schott

The Use of Vitamin E in Heart Disease. S. BAER, W. I. HEINE, and D. B. GELFOND. *Amer. J. med. Sci.*, **215**, 542–547, May, 1948.

The effect of vitamin E orally in doses of 300 to 400 mg. daily was observed in 22 patients with various forms of heart disease. The authors conclude that, although their numbers are few, they cannot, from the evidence, recommend vitamin E in the treatment of congestive heart failure, angina pectoris, or hypertension.

C. Bruce Perry

Andreno-sympathogenic Heart Disease (Neurohormonal Factors in Pathogenesis and Treatment). W. RAAB. *Ann. intern. Med.*, **28**, 1010–1039, May, 1948.

The author points out that mechanical overload is not necessarily the whole explanation of hypertensive heart disease. Many of the features of hypertensive heart disease may be found without hypertension. He calls attention to the possible pathogenic role of adrenaline and allied substances. Adrenaline intensifies the oxygen consumption of the heart, and may induce a state of anoxia, identical with experimental anoxia in diseased human hearts and in animal hearts after severe exercise. The author considers that anginal attacks are accompanied by abnormal elevation of the adrenaline sympathin levels in the blood. Hypertensive heart disease is not necessarily accompanied by any rise in adrenaline level in the blood, but abnormally high elevations of the levels of this and similar substances may follow physical exercise in patients with hypertension. The electrocardiographic features of hypertensive heart disease are similar to those which result from the injection of adrenaline, and it is emphasized that the abnormal electrocardiogram may revert to normal after sympathectomy, even if the patient remains hypertensive. The author develops similar arguments to account for changes in the heart in uræmia, thyrotoxicosis, and beriberi. These arguments are supported by a very extensive bibliography of 235 references. *J. McMichael*

Endocardiac Potentials in Right Heart Hypertrophy. Comparison with the Oesophageal Electrocardiogram. P. SCHLESINGER, A. BURLAMAQUI ENCHIMOL, and M. R. COTRIM. *Arch. Clin.*, **6**, 139–155, March, 1948.

Battro and Bidoggia have drawn attention to the similarity of the ventricular complex with the electrode in the right auricle and with the œsophageal lead in both healthy and diseased subjects. This paper deals with 5 cases of right-sided hypertrophy. The electrode, attached to a fine insulated wire, is introduced through the right external jugular vein, "sodium amytal" being used as premedication. There were no untoward effects, penicillin being given subsequently for 48 hours. Standard, unipolar, and præcordial leads, and leads with the electrode at different intra-auricular and intra-ventricular levels were taken. The P wave is negative with the electrode at a high auricular level and gradually becomes positive as the electrode passes into the ventricle; the QRS complex at auricular level was positive in 3 cases and negative in 2. The ST segment was elevated in 3 cases when the electrode was in the ventricle. The œsophageal leads, taken at auricular level, were found to have QRS complexes similar to those taken at intra-auricular level. Very similar complexes were also found with the unipolar VR lead. Some anomalous changes were thought to be due to the impulse passing over the wall of the interventricular septum. *Paul B. Woolley*

Influence of Hypotension on Coronary Blood Flow, Cardiac Work and Cardiac Efficiency. J. E. ECKENHOFF, J. A. HAFKENSCHIEL, E. L. FOLTZ, and R. L. DRIVER. *Amer. J. Physiol.*, **152**, 545–553, March, 1948.

In lightly anæsthetized intact dogs, coronary blood flow was measured by the nitrous oxide method, coronary sinus blood being obtained by catheterization. Cardiac output was estimated by the direct Fick method. Hypotension was produced either by the subarachnoidal injection of procaine solution or the intravenous injection of tetræthylammonium chloride. A decrease in cardiac output and cardiac work (cardiac output × aortic pressure) occurred. Coronary blood flow decreased but the rate remained relatively high in relation to the decreased work. Cardiac efficiency (work/oxygen consumption) was reduced but there was no evidence that the heart was less able to perform the work required of it, that is, that the hypotension was harmful to the heart.

R. A. Gregory

The Course of Beriberi Heart Disease in American Prisoners-of-war in Japan. R. J. ALLEMAN and G. H. STOLLERMAN. *Ann. intern. Med.*, **28**, 949–962, May, 1948.

It is generally thought that heart disease due to beriberi is accompanied by right heart enlargement and manifestations of a rapid circulation, and that a response to aneurin (thiamin) therapy is diagnostic. More recently, the diagnosis has been made when there is evidence of gross dietetic deficiency together with peripheral neuritus in the presence of an enlarged failing heart for which there is no other explanation. Even failure to improve with aneurin does not exclude the diagnosis. Should the heart respond well to the specific vitamin relapses may still occur.

Two cases are described. In the first, there was a gross nutritional inadequacy, with widespread œdema, cramps in the legs, and incoordination. The patient improved on treatment with the ordinary cardiac remedies, with aneurin, but very quickly relapsed. A further improvement occurred for a time, but in a third attack he died. Apart from some degeneration of the myocardial fibres and infiltration with small round cells, no other explanation of the failure was found at necropsy. In the second case the onset was similar, but the patient made a good recovery when given an adequate diet and large doses of vitamins orally and parenterally. The symptoms cleared up at the end of 4 months.

J. McMichael